

Early detection of cancer. A new branch of oncology?

Diagnosi precoce dei tumori. Una nuova branca dell'oncologia?

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Summary

Cancer mortality has started to decrease in the Western World. The rôle played by early detection in this decrease is a matter for debate. To assess the impact on mortality it is important to distinguish between diagnosis of cancer in symptomatic patients, and early detection in asymptomatic individuals who may self-refer or who may be offered ad hoc or systematic screening. The policies for early detection and screening vary greatly between European countries, despite many similarities in their cancer burden, and this partly reflects the uncertainties surrounding asymptomatic testing for cancer. For some cancers such as those of the breast, mass screening programmes actively promoted by health authorities at a local or national level vary in their impact on cancer mortality reduction. The European School of Oncology has set up a special Task Force to address these issues, in particular the growing demand for early detection, and the first report is presented here. The task force brought together representatives from several European countries. The group recognised that combinations of early detection and screening will enforce the effectiveness of new treatments in curbing mortality curves, although policies will vary with different cancers. With the growing demand for early detection, there is a great need for cultural and scientific efforts towards structuring early detec-

Riassunto

La mortalità per cancro ha cominciato a diminuire nel mondo occidentale. Il ruolo della diagnosi precoce in questa riduzione è oggetto di discussione. Per determinare l'impatto sulla mortalità è importante distinguere tra la diagnosi di cancro nei pazienti sintomatici e la diagnosi precoce negli individui asintomatici che si presentano spontaneamente o nell'ambito di uno screening ad hoc o sistematico. Le strategie per la diagnosi precoce e lo screening variano notevolmente nell'ambito di vari paesi europei, nonostante molte similitudini per quanto riguarda l'incidenza dei tumori, e questo riflette in parte le incertezze sugli esami per diagnosticare i tumori asintomatici. Per alcuni tumori, come quelli della mammella, l'impatto dei programmi di screening di massa, promossi dalle autorità sanitarie a livello locale o nazionale, sulla riduzione della mortalità da cancro, è variabile. La Scuola Europea di Oncologia ha istituito una speciale Task Force per affrontare questi problemi, in particolare la richiesta crescente di diagnosi precoce, e qui viene presentato il primo resoconto. La Task Force raccoglie rappresentanti di diversi paesi europei. Il gruppo ha riconosciuto che la combinazione di diagnosi precoce e screening aumenterà l'efficacia di nuovi trattamenti nell'influenzare le curve di mortalità, sebbene le strategie siano diverse per i diversi tipi di tumore. Essendoci una domanda crescente di diagnosi precoce, c'è una crescente necessità di sforzi culturali e scientifici orientati ad impostare la diagnosi precoce come competenza specifica (se non disciplinaria) ed a collegarla alla medicina preventiva. Per far fronte a questa domanda crescente, una soluzione potrebbe essere quella di offrire la diagnosi precoce dei tumori mediante ambulatori dedicati e non mediante ospedali, dato che l'ospeda-

tion as a specific competence (if not discipline) and linking it to preventive medicine. To cope with rising demand, one solution would be to promote early detection of cancer (EDC) preferably by specific outpatients clinics and not by hospitals, since the hospital is already related, in a psychological sense, to the concept of illness. Health professionals working in EDC should also receive specific training since the challenge facing them is not that of deciding whether a given lesion is, or is not, cancer, but rather whether or not an apparently healthy individual has cancer. The clinical approach to the healthy person who wishes to know their probability of already having cancer or the possibility of cancer developing in the future is very different from the traditional treatment-oriented attitude of oncologists. It is an approach which calls for different clinical and psychological skills. *Eur. J. Oncol.*, 8 (3), 165-175, 2003

Key words: early detection, cancer, healthcare services

Introduction

There is a growing demand – at least in the Western World – for specific services and procedures aimed at the prevention of cancer, or at the very least, ensuring early detection in order to maximise the chances of cure.

As a consequence of awareness campaigns promoted through the media by cancer charities and associations on both sides of the Atlantic, people are increasingly ready to change their lifestyle and to adopt preventive measures to avoid cancer (or at least death by cancer). The concept of “individual cancer risk assessment” has gained favour mainly as a result of the seminal work conducted by Mitchell H. Gail for breast cancer¹. In addition other mathematical models have now even been made available on the Internet².

However the need people feel to “do something” to avoid cancer death is not in general met by oncology services today. It is quite common in Europe to hear of women who were told about the importance of having a mammography and then found themselves confronted with huge waiting lists impeding their access. Another major complaint is the difficulty of concentrating the examinations into one single day and location. It can prove excessively time-consuming to undergo a mammography, PAP smear, nevi check-up and ORL examination at one and the same time (as in the case of a postmenopausal woman, who smokes ten cigarettes a day and wishes to leave for a two week holiday in the sun).

Finally, who will pay for early detection of cancer (EDC) and what evidence is there that this approach has a positive cost/benefit ratio?

Our group decided to concentrate on a set of sound, feasible and well-tested recommendations to those considering setting up clinics for the early detection and prevention of cancer.

An important and similar effort was already made in 2000 by the American Cancer Society³ and the present paper aims to accelerate the debate on this topic, particularly in Europe.

Lung cancer

Lung cancer is the most common cancer in the world today (12.3% of all new cancers). There were estimated to be 1.2 mil-

le è di per sé collegato, sotto l'aspetto psicologico, al concetto di malattia. Inoltre gli operatori sanitari impegnati nella diagnosi precoce dovrebbero ricevere un addestramento specifico, dato che il problema che si trovano ad affrontare non è quello di decidere se una data lesione è cancro o no, ma se un individuo apparentemente sano ha un tumore o no. L'approccio clinico ad un individuo sano che vuol sapere quale probabilità ha di avere già un tumore o di sviluppare un tumore in futuro è molto diverso dal tradizionale atteggiamento degli oncologi orientato al trattamento. È un approccio che richiede capacità cliniche o psicologiche diverse. *Eur. J. Oncol.*, 8 (3), 165-175, 2003

Parole chiave: diagnosi precoce, cancro, servizi sanitari

lion new cases in 2000, 52% of which occurred in the developed countries. Recently lung cancer has eclipsed breast cancer as the leading cause of cancer death in women. Tobacco smoking is by far the most important cause of lung cancer. The overall 5-year survival rate for lung cancer patients is approximately 15%. This is due, in the majority of cases, to the advanced stage at which the disease is detected. However, with early diagnosis, aggressive surgical therapy, and even intervention such as laser or electrocauter therapy in selected cases, 5-year survival rates can approach 60% for early stage disease.

Early lung cancer detection

Early lung cancer (ELC), non-small-cell type, can be broadly divided into two categories: peripheral or radio-opaque, and central or radio-occult. With some overlap, the distinguishing features of peripheral and central lesions are, respectively, prevalence, 60% : 40%; histogenesis, adenocarcinoma : squamous cell carcinoma; and prognosis, worse : better. The major tools available for ELC detection are low-dose spiral CT for peripheral lesions and sputum cytology and automated cytometry as well as conventional combined with auto-fluorescence bronchoscopy for central lesions⁴. Biomarkers, using high-throughput genomic and proteomic technologies, may prove useful for both central and peripheral tumours. Biomarkers include microsatellite instability, loss of heterogeneity, and aberrant methylation⁵. These procedures are currently being tested in large clinical trials worldwide. A fundamental question centres on whether public health policy decisions on ELC screening should await the outcome in 5-10 years, or whether some procedures for ELC detection should be offered to susceptible patients even as the trials continue. Our response to this predicament is two-fold.

In many recent case-finding studies, these procedures (with the exception of biomarkers, which are still in the early validation phase) have been shown to increase the number of early-stage lung cancers detected, when compared to non-screened statistics. Hence it would seem unjust to deprive all high-risk patients of these diagnostic tools for the many years necessary before the final results of trials in progress become available, and we therefore offer this service to such patients if not participating in the trials.

Many trials of low-dose spiral CT are in progress. Our own emphasis is on the central type ELC, and the RIDTELC Lung Study aims to validate the use of induced sputum cytology, automated sputum cytometry, conventional and auto-fluorescence bronchoscopy, and the use of biomarkers, in a controlled trial of 6000 heavy smokers aged 50-74. Baseline and incidence studies are done at $t=0$ and repeated at $t=36$ months, with identical annual, postal monitoring for incidental respiratory symptoms. Tentative results in the treatment group following recruitment and randomization of 2000 volunteers show a lung cancer prevalence of 1.2% with a significant shift to Stage 0, Stage I and Stage II disease.

The results from another study, the Early Lung Cancer Action Project (ELCAP) were recently published⁶ showing that low-dose CT can greatly improve the likelihood of detection of small non-calcified nodules and thus of lung cancer at an earlier and potentially more curable stage.

Comment

From a public health standpoint, lung cancer is unique among the leading cancers, because the underlying causal factor responsible for approximately 87% of cases is well-known and for the most part avoidable. Despite this many adults are current or recent smokers, and a significant percentage of children still take up smoking. At the time of writing, there is no organization which recommends routine screening for lung cancer among the general adult population, or for individuals who are at higher risk due to tobacco or occupational exposure.

In view of the promising results from investigations with spiral CT and other early detection tests (e.g. biological markers in the sputum), the International Task Force strongly suggests screening for lung cancer in high risk patients (e.g. age ≥ 50 yrs, ≥ 20 cigarette/die for 20 yr). A move towards routine screening would represent a fundamental change in the approach to lung cancer, and the potential benefits of early lung cancer treatment could be enormous.

Prostate cancer

Prostate cancer is now the sixth most common cancer in the world (in terms of number of new cases), and the third in men. However in the Western world it is the most common cancer. The total annual number of cases is 513,000, i.e. 9.7% of cancers in men. Prostate cancer rarely occurs before the age of 50 years; the incidence increases through the ninth decade of life. Thirty per cent of men older than 50 years with no clinical evidence of prostate cancer will demonstrate a focus of cancer within the prostate at the time of autopsy.

Early detection of prostate cancer

Prostate specific antigen (PSA) was the first Food and Drug Administrations (FDA) approved tumour marker for the early detection of prostate cancer and has been employed since 1994. For screening, PSA should be used as a first line test. There are as yet no general guidelines for screening or biopsy use⁷.

As one of the main points of this Task Force meeting, we conclude that at least a six-core biopsy, including a repeat biopsy within 3-6 months, should be performed if there is a risk of prostate cancer.

Within the PSA ranges 4-10 ng/ml (90 or 95% sensitivity) and also 2-4 ng/ml (90 or 95% specificity) the ratio of free to total PSA can increase the rate of detected cancers per biopsy⁸. Neural networks using PSA, free PSA and additional clinical data such as age and prostate volume are recommended to further improve the cancer detection rate. Our developed programme "ProstataClass" can further increase the specificity at given sensitivities by 20-30%⁹.

Other molecular forms of PSA such as complexed PSA, alpha-2-macroglobulin PSA or alpha-1-protease-inhibitor PSA are unlikely to improve specificity over free PSA. Subforms of free PSA such as proPSA, BPSA or intact PSA are still undergoing research and have yet to be tested in large cohorts¹⁰.

Preliminary investigations are underway into another member of the kallikrein family, human glandular kallikrein 2 (hK2), which could yield substantial additional information and prove valuable in detecting prostate cancer, especially at low PSA values. Other members of the expanded human kallikrein family may also add clinical information for early detection of prostate cancer¹¹. Until now, the Gleason grade 4/5-cancer volume has been the only independent predictor of biochemical failure after radical prostatectomy. Therefore new markers indicating cancer progression are urgently needed. Current microarrays are capable of identifying genes which are overexpressed in prostate cancer. Antibody production for these related proteins may open up new ways for the development of serum markers.

Comment

The recent trend in prostate cancer incidence is characterised by a dramatic increase in incidence rates beginning in the mid-1980s and peaking in 1993. This is mostly due to the introduction of PSA testing for early prostate cancer detection. The five-year survival is nearly 100% when the disease is diagnosed at a local or regional stage, but poor when the disease is diagnosed with distant metastases (32.6%). In the light of new data arising from ongoing studies we suggest that PSA and digital rectal examination (DRE) be offered annually beginning at the age of 50 years. Men at high risk should begin testing at 45 years. From the promising preliminary results, we recommend further evaluation of the "ProstataClass" programme which may increase the specificity still more.

Cancer of the stomach

Gastric cancer, that, even in the western countries, has shown a decreasing slope in the last 50 years, is on a worldwide basis the fourth estimated tumour with 876,000 new cases, and estimated year deaths n. 647,000 during the year 2000. Almost 2/3 of the tumours occur in the developing countries with wide variations between borderline areas.

North America is at low risk, while Japan, eastern Asia and South America are, on the contrary, highly involved.

Incidence in the male sex is anyhow twice than in females except in the younger age group.

Adenocarcinoma, with intestinal type prevailing in the high incidence countries, is the most common histologic feature; a marked increase of cancer in the cardia (related to the prevalence of Barrett's oesophagus) is observed in the same geographical areas. The high malignancy and drug-resistance of the gastric can-

cers, strongly require an adequate surveillance and possibly an aggressive potentially curative surgical approach.

Dietary risk factors and *Helicobacter pylori* infections causing atrophic gastritis are involved in the pathogenesis of gastric cancer, therefore a screening for early disease diagnosis is related to endoscopic protocols in high risk or symptomatic population¹².

Gonvers *et al*¹³ suggest as definite surveillance criteria: anaemia, high grade gastric mucosa dysplasia, familial adenomatous polyposis, hereditary colorectal non polyp-born cancer and adenomas, as well as HP infection, chronic atrophic gastritis and intestinal metaplasia.

Comment

The frequency of endoscopy is reasonably stated every 2 years, but interval follow-up with less invasive methods in order to detect precancerous conditions on larger population cohorts should be relevant as a screening, thus delaying endoscopic manouevres every 3-5 years.

Balloon cytology screening for Barrett oesophagus¹⁴ and for oesophageal cancer in general¹⁵ has been successfully applied as a screening method in this upper GI segment.

We are now developing a simple not invasive device suitable for sample collecting fluid from the gastric cavity (Gastrotest) that might give some sort of "point of care" information about gastric physiopathology.

This very easy and scarcely invasive procedure should be applied at doctor's surgery level and even if less accurate than endoscopy because of the high patient compliance can be repeated several times in the intervals.

Colorectal cancer

Colorectal cancer comprises 13% of all cancers and is responsible for 10% of all cancer deaths. The age incidence of colorectal cancer increases steadily from the second through the eighth decades of life, with a male predominance. At diagnosis, 10% of patients have *in situ* disease, one-third have local disease, and one-third regional disease; 20% of patients have distant disease. The overall 5-year survival rate for colorectal cancer is 50%. However, when stratified by local, regional, and distant disease, the survival rates are 90%, 58%, and 5%, respectively.

Early detection of colorectal cancer

There is now solid evidence from randomized trials suggesting that it is possible to reduce mortality from colorectal cancer by 15%-25% by screening with faecal occult blood tests (FOBTs)¹⁶. The major benefit results from the detection of early cancer in average-risk persons above 50 years of age, who have a positive test followed by colonoscopy. However, it has to be demonstrated whether the same acceptability can be reached in the general population as that obtained in trials. Screening organizations in limited areas are needed to learn how satisfactory quality assurance can be obtained before a country-wide screening programme is set up. So far, screening has not resulted in a reduced incidence of colorectal cancer in true population studies, despite removal of two to three times as many possible precursors compared to controls. Cost-effectiveness will probably be as good as that from screening for breast cancer with mammography and better than

that for cervical cancer. However, the calculations are based on the unhydrated Hemoccult-II test in randomized trials. More sensitive methods would be attractive, but none has yet been evaluated properly in average-risk persons.

The major possible alternative to FOBT is flexible sigmoidoscopy (FS). The flexiscope trial consists in evaluating a one-off FS followed by colonoscopy when high risk adenomas are detected. The aims of the trial are to test the efficacy, practicality, acceptability and safety of the process¹⁷. Individuals were sent hypothetical invitations to attend FS screening, and 53% responded that, in theory, they would be interested in taking part. One third of these were randomised to an intervention group. All these individuals were then sent real invitations: 71% of these actually attended screening (38% of the population in total). Interestingly, more men than women accepted the invitation to attend.

The FS trial hopes to produce positive results at the same time as the FOB pilot evaluation is published, in order that governments can make an informed choice about which (if any) colorectal cancer screening programme to implement.

The future of colorectal cancer screening would include better FOB tests with increased sensitivity, but maintaining specificity. New immunological tests are being developed, opening up the possibility of automation of testing¹⁷⁻¹⁹. DNA tests may also be developed.

Melanoma

Although melanoma is a relatively uncommon malignancy worldwide, its incidence has shown a dramatic increase (150%) since 1971. Melanoma incidence is similar in men and women and increases from the age of 10 years to the fifth decade. Approximately 1 in 123 Caucasians will develop melanoma in their lifetimes; lifetime risk is expected to be 1 in 90 by the year 2010.

Early detection of melanoma

In most countries, the incidence and mortality rates for malignant melanoma are low when compared with those of other tumours such as lung, breast and prostate cancers. Therefore the general population screening for melanoma is neither practical nor cost-effective. However, interest remains in early detection for the following reasons:

- 1) the incidence of melanoma starts to rise after the age of 25 years, and a higher number of deaths from melanoma occur under the age of 60 than for most other cancers;
- 2) the greater the depth of cancer growth (Breslow thickness) the poorer the survival, so it is believed that the sooner the cancer is detected, the greater the possibility of cure;
- 3) thin melanomas can be removed by simply excision using a local anaesthetic; they are thus inexpensive to treat, and have minimal effect on the quality of life.

Alternative options to general population screening have been studied. These include the following: health education to enable the general population to become aware of the early signs of melanoma, in order to have a timely diagnosis, targeted screening of high risk groups and opportunistic screening²⁰⁻²⁴. In the UK, a publicity campaign to promote early detection in the general population was launched, first in the West of Scotland²¹ and then in seven areas of England and Scotland²². There was no conclusive evidence from either study that this method resulted in a reduction

in melanoma mortality. However, the initial phase of each campaign did increase the staff workload and the detection rate of thin melanomas. Clinics for pigmented lesions were set up during the campaigns to cope with the extra workload, and some hospitals still have such clinics to ensure a quick referral of lesions with a suspicion of melanoma.

Targeted screening can focus on very high risk groups such as those with a family history of the disease²³ or those with a phenotype which carries a higher risk than the average population, such as those with fair skin or a large number of nevi²⁴. Methods for identifying people with specific phenotypes have been investigated²⁵⁻²⁷. In one study²⁸ the answers to a questionnaire completed by the general population were compared with a dermatologist's assessment of the same people attending a skin clinic. People tended to underestimate their level of risk factors, e.g., they would report fewer moles than the number identified by the dermatologist, so the questionnaire approach did not seem to be reliable. It was also found that knowledge of the early signs of melanoma was poor, suggesting that health education could be improved. Opportunistic screening has been studied, for example, when buses have toured different sites and people have been offered information and a skin check-up^{29,30}.

To improve the early detection of melanoma, it is also important to study the reasons for diagnostic delay. This may partly occur because individuals do not recognise early signs on their skin, the general practitioner (GP) fails to recognise or diagnose the cancer, and dermatological counselling in the hospital is delayed³¹⁻³⁴. Strategies are needed to improve the recognition by GPs of suspect lesions deserving diagnostic aids, to ensure swift referral of suspect lesions, and to evaluate the rôle of pigmented lesion clinics^{31,32}.

Comment

As melanoma is a visible skin lesion, its diagnosis does not require invasive procedures. Moreover, removal of melanoma at an early stage cures the disease. Therefore, melanoma is potentially eradicable. Despite this apparent simplicity, the best strategy for detecting melanoma at an early curable stage is still a matter of debate. Recent studies have shown that the observation of less and less thick melanomas over time in many groups of people seems attributable to increasing awareness and spontaneous skin surveillance. Nevertheless, large-scale population screening would be costly and probably offer little advantage in terms of extra years of life. However, further efforts are needed for early detection. In fact, the absolute number of thick melanomas remains unchanged, mainly in older men. Promotion of skin surveillance should be given priority in older people as well as in known high-risk subjects.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a neoplasm with an increasing incidence worldwide³⁵. Liver cancer is the fifth most prevalent human tumour and the third cause of cancer-related death in the world³⁵. It is one of the few human cancers in which the main aetiological risk factors have been identified. Liver cirrhosis, mainly due to viruses (hepatitis B and C infections), constitutes the main risk factor, the 5-year cumulative incidence in

these patients ranging between 15% to 20%³⁶. Despite the wide implementation of surveillance programmes in Western countries, only 30% of HCC patients may receive potentially curative therapies; this figure decreases substantially when considering population-based registries³⁷. Thus, HCC constitutes a major health-care problem.

Risk factors and cancer prevention

Cirrhosis is the main risk factor for HCC development, and underlies the neoplasm in 90% of cases in Western countries³⁶. Amongst cirrhotics, hepatitis-B virus (HBV) and hepatitis-C virus (HCV) infection and alcohol intake are associated with the highest risk. Conversely, in Africa and Asia, where the HBV infection is acquired early in life and coincides with other oncogenic agents (i.e. aflatoxin), HCC may develop in around 40% of cases in a non-cirrhotic liver. Worldwide, the annual incidence of HCC in non-cirrhotic HBV patients is 0.4-0.6%, whereas in HBV-related cirrhotic patients it is 2%, and reaches 3-8% in HCV-related cirrhosis³⁶.

Cancer prevention may be attempted at three levels. Primary prevention aims at preventing exposure to the main carcinogens from initiating the carcinogenic process. This can be partially achieved with HBV vaccination programmes³⁸ or with health-care counselling, and also by avoiding aflatoxin contaminated food. Secondary prevention deals with disrupting of the progression from chronic hepatitis to cirrhosis. Patients with chronic hepatitis C may achieve sustained virological responses in 40-60% cases by using the combination of pegylated-interferon and ribavirin, thus preventing progression to cirrhosis. Similarly, in patients with chronic hepatitis B, lamivudine and adefovir are effective. These treatments decrease the proportion of patients developing cirrhosis, and this should reduce the incidence of HCC. Tertiary prevention refers to the prevention of HCC development when cirrhosis is established. This issue has only been assessed in two randomized controlled trials (RCTs), which included a small number of individuals and yielded contradictory results. Thus, large RCTs with the specific end-point of HCC prevention are needed³⁶.

Surveillance and prognosis of HCC

The prognosis of HCC patients varies according to the evolutionary stage at which the neoplasm is diagnosed³⁷. Early diagnosis is feasible in surveillance programme settings, from which radical therapies can be embarked on. A proper selection of candidates for resection, liver transplantation and percutaneous treatments provides 5-yr survival rates ranging between 50% and 70%^{37,39,40}, whereas the best natural history of the disease reported 5-yr survival rates of 15-20%⁴¹. Therefore, it is assumed that radical therapies modify the natural course of the neoplasm, and reinforce the need for anticipating the diagnosis of early tumours.

Surveillance for HCC meets some of the standard criteria for instituting a cost-effective programme for any disease³⁸. HCC occurs frequently in some populations at risk, it induces a significant morbidity and mortality, the population at risk accepts the need for screening, and physicians generally do believe that surveillance is necessary. However, the surveillance tests are imperfect, and recall procedures are not well established. Finally, although therapy is not highly effective, it is curative in some patients. Sur-

veillance is thus the only strategy to potentially decrease tumour-related mortality, since it may detect HCC at an early stage, when curative therapies can be applied. There are no RCTs comparing surveillance with nonsurveillance. Cohort studies and cost-efficiency modelling bear out the benefits in well-defined candidates, mainly Child-Pugh's A class cirrhotics, who would merit effective treatment if diagnosed with HCC. This discards advanced cirrhotics (Child-Pugh's C class) and those with severe associated conditions. Data on tumour volume doubling time give the rationale for the current recommended surveillance policy: echography and AFP determination every 6 months. Applying this policy, 40-80% of HCC detected are single lesions, but only half of them are radically treated³⁹.

From the available clinical data, the European Association for the Study of the Liver (EASL) advises the scheme of surveillance and recall policy presented in fig. 1³⁶. This strategy provides a common guide for early detection and diagnostic confirmation of HCC. Diagnosis of HCC is based on cyto-histology, but reliable non-invasive criteria for cirrhotic patients are proposed. HCC may be certainly diagnosed by the contemporary findings of two imaging techniques showing a nodule > 2 cm with arterial hypervascularization, or by a single positive imaging technique associated with AFP > 400 ng/mL³⁶.

Comment

Early diagnosis of HCC has become the key factor in increasing the applicability of those curative therapies which offer the best chance for improving the life expectancy of such patients. The objective of these programmes is to reduce the disease specific mortality. Surveillance programmes for early detection of HCC should be addressed to a well-selected population at risk. Several epidemiological studies have also shown that the main risk factors for HCC are older age, male gender and cirrhosis of any aetiology, mainly related to chronic HBV or HCV infection, or alcohol, which is the most important factor. In Europe, cirrhosis underlies HCC in more than 90% of cases. According to these data, clinic-based programmes should be conducted in cirrhotic patients. Implementation of screening programmes in non-cirrhotic patients would probably not lead to a potential benefit. The

restrictive criteria of age, stage of liver disease or baseline conditions that would preclude radical therapies should be assumed when early detection is organised.

Gynaecological cancers

Gynaecological tumours affect six different sites: ovary, Fallopian tube, endometrium, cervix, vagina and vulva.

Endometrial carcinoma

Endometrial carcinoma accounts for approximately 13% of malignancies in woman and ranks fourth in frequency behind breast, lung and colon carcinomas. While endometrial carcinoma is primarily a postmenopausal disease, with a median age onset of 63 years, up to 25% of cases occur in premenopausal women, with 5% occurring in patients younger than 40 years.

Early diagnosis of endometrial cancer. Atypical genital bleeding in menopause represents an early symptom, permitting diagnosis to be made in the initial stages of the disease, with a good prognosis; no screening test will be found to decrease mortality in this clinical setting. Even in high risk groups (hormonal replacement treatment or tamoxifen users) evidence of mortality reduction from screening is lacking. Endometrial thickness as assessed by transvaginal ultrasounds allows a reduction in endometrial biopsy rate but only in symptomatic patients.

Cervical carcinoma

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 468,000 new cases and 233,000 deaths in the year 2000. Almost 80% of the cases occur in developing countries where, in many regions, it is the most common cancer among women. The incidence of cervix cancer begins to rise at age 20-29 years, and the risk increases rapidly, reaching a peak usually around the age of 45-49 years in European populations.

Early diagnosis of cervical cancer. Cytological screening has demonstrated a cost-effective reduction in cancer incidence and mortality; pre-cancer detection is also achieved by periodic screening. Effective screening is mainly dependent on the system as a whole, organisation, quality control and patient communication.

The possibility of detecting and treating cancer precursors through screening intensification (annual pap-test) and combination of other cervical pre-cancer detection exams remains an open issue. There are no data on this policy, even if this practice is well accepted among gynaecologists. In this area patient information, management protocols and standard indicators are necessary but still lacking. Finally, the very high negative predictive value of HPV testing looks promising for patient reassurance.

Ovarian cancer

Carcinoma of the ovary is the fourth most common cause of death from cancer in women, accounting for 5% of all cancer-related deaths. Approximately one-quarter of all gynaecologic malignancies are of ovarian origin, and 47% of all gynaecologic can-

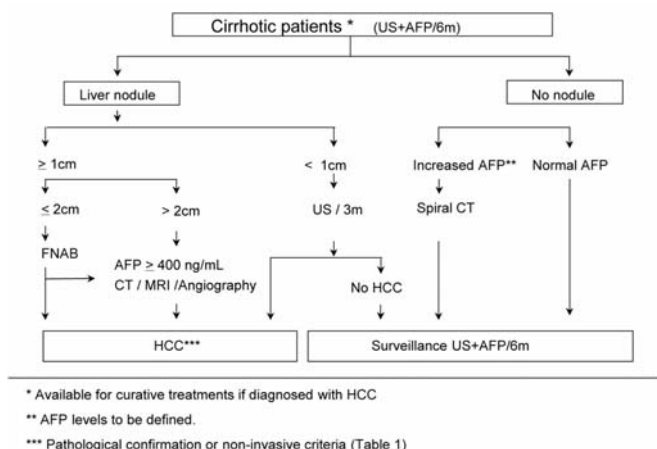


Fig. 1. Surveillance and recall strategy for HCC.

cer-related deaths are due to ovarian cancer. This is primarily because the disease frequently remains undiagnosed until an advanced stage.

The lifetime risk of developing ovarian cancer is approximately 1 in 70. Incidence increases with age and peaks in the eighth decade of life.

Early diagnosis of ovarian cancer is complicated by the fact that it is a disease with an unknown natural history. Occasional reports have shown a very rapid (less than three months) onset of advanced disease. Transvaginal ultrasound represents an efficacious diagnostic test, but the low specificity of the results plus the need to access the abdominal cavity as a second level investigation are factors of major concern when the test is applied in early detection and prevention settings. The use of serum marker CA125 for ovarian cancer screening is under investigation in large randomized population studies⁴².

Vulvar neoplasms

They are rare and require only a careful inspection of the external genitalia by the patient or physician: information and awareness are key factors for early diagnosis.

Vaginal cancer

They are very rare neoplasms, and the pap smear generally diagnoses them as cervical cancers.

Tubal neoplasms

They are rare tumours diagnosed by ultrasound.

Comment

Most gynaecological tumours comprise cervical, endometrial and ovarian cancers; concerning prevention and early diagnosis they represent three different models (Table 1).

Since profound differences exist between evidence based screening and clinical practice, for each test it is advisable to set specific recommendations for subsequent patient management and quality standards. Patients and physicians should be fully in-

formed on the aims, risks and benefits of undergoing testing outside evidence based screening systems.

Carcinoma of the head and neck

Approximately 67,000 cancers of the head and neck are diagnosed in the United States each year. The relative frequencies of primary head and neck tumours by site are: 40% in the oral cavity, 25% in the larynx, 15% in the oropharynx, 7% in the major salivary glands, and 13% in other sites. The male to female ratio is 3:1, and the average age at onset is approximately 50 years.

There is an increased incidence of squamous cell carcinoma (SCC) in patients with heavy tobacco and alcohol exposure.

Early detection of head and neck cancer

Head and neck tumours comprise a heterogeneous group of tumours of different origins and biological properties. However, an overwhelming proportion of these tumours are represented by skin tumours and by tumours of the mucous membrane of the oral cavity, pharynx and larynx, while tumours of salivary glands and the thyroid are rarer.

Notwithstanding their origin, all these tumours have one thing in common: their early identification is of extreme importance for the patient's outlook and survival. Tumours identified early enough permit treatment procedures that are less demanding for the patient and bring about less undesirable side effects^{43,44}. At the same time, they offer the patient a greater degree of hope for a permanent cure. However, most of these tumours are diagnosed only at an advanced stage. This is why we have been looking for ways and means to increase the percentage of patients diagnosed at an early stage.

Head and neck tumours are relatively infrequent, accounting for some 5 percent of all tumours.

Because of this low rate of incidence, head and neck tumours are not in the forefront of across-the-board preventive medical programmes. Nevertheless, patients wishing to undergo preventive medical examination to check for a potential tumour can be recommended to have an ORL examination as well.

The ear, nose and throat (ENT) examination is a relatively inexpensive, readily available and patient-friendly procedure. As most head and neck tumours are superficial formations on mu-

Table 1 - Gynaecological tumours: present status

Site	Screening (evidenced-based)	Screening under investigation	Clinical practice
Cervix	Every three years pap smear, ages 25 to 65	HPV testing to increase interval screens	Annual pap smear +/- other tests; gynaecological exam
Endometrium	No screening test	None	Transvaginal ultrasounds; gynaecological exam
Endometrium high risk (hormone replacement therapy, tamoxifen)	No screening test	Transvaginal ultrasounds; medicated IUD	Annual transvaginal ultrasounds; gynaecological exam
Ovary	No screening test	CA125	Transvaginal ultrasounds; gynaecological exam
Ovary high risk (hereditary)	No screening test	None	Genetic test; prophylactic oophorectomy in selected patients

cous membranes in the head and neck area, and because of the good accessibility of these mucous membranes for examination, it is possible to identify most of the tumours in this area at a sufficiently early stage. Consequently, the basic ENT examination is sufficient as a preventive and screening examination for head and neck tumours. As a rule, the recommended interval is 6 to 12 months.

While ENT examinations do not have a fixed place in preventive programmes focusing on the general population, regular preventive ENT examinations can definitely be recommended insofar as regards the segment of male smokers over 40, who also possibly consume increased quantities of alcohol. The population segment referred to above is in fact particularly at risk from the viewpoint of head and neck carcinomas. Unfortunately, these patients are generally less willing to take part in preventive programmes.

Although the head and neck area is one which offers relative ease of access for the purpose of examination, thus providing good prerequisites for early identification of tumours, some two-thirds of these tumours are identified at a fairly late stage. This situation is attributable to the fact that patients are late presenting themselves for examination; the tumour shows a fairly rapid progress and, at the same time, there are relatively few alarming symptoms in the early stage of the tumour ailment, which patients often mistake for feelings of discomfort associated with acute or chronic inflammations of the upper respiratory tract. In this respect, the general practitioner or dentist also play an important rôle in the early identification of tumours in addition to the obvious rôle of the otorhinolaryngologist. Every stomatological check-up includes a preventive oncological examination of the oral cavity. Similarly, every patient who suffers from hoarseness, swallowing pains or discomfort for a period in excess of three weeks and who does not respond to routine treatment should be referred by the general practitioner to a specialist: every patient visiting an otorhinolaryngologist should undergo a comprehensive ENT examination to rule out an early tumour.

In addition to the basic ENT examination focusing especially on mucous membranes, every preventive check-up should include an examination of the skin of the head and neck.

The skin is the most frequent tumour site on the human body. Most skin tumours are found in areas exposed to solar radiation, i.e. often in the head and neck area. Spinocellular and basocellular skin carcinomas are typical for groups of patients at advanced age, and these involve a relatively good outlook for the patients.

When examining the oral cavity, it is necessary to inspect all of the mucous membranes and supplement this inspection by a palpation of the tongue and the floor of the mouth. When examining the oropharynx, particular attention should be paid to the tonsils and the root of the tongue. Indirect laryngoscopy is employed to examine the tongue base and valleculae. When examining the tonsils and tongue base, palpation is a very useful tool, as it often permits an early identification of an endophytic carcinoma which visual methods are capable of identifying only at the ulceration stage.

The larynx and the hypopharynx are examined by indirect laryngoscopic methods, i.e. using a mirror. In this respect, the purpose is to identify whatever changes may have occurred on the mucous membranes of the larynx and particularly in the vocal chords, to assess the freedom of movement of the vocal chords, and to determine whether the pyriform sinuses are empty and do not contain any stagnant saliva.

The nasopharynx and nasal mucous membrane examination, which is a part of the basic ENT check-up, makes use of posterior and anterior rhinoscopy. In the event of an ambiguous or pathological finding, examination of the nasal cavity and nasopharynx is supplemented by rigid rhino-epipharyngoscopy; and if considered necessary, a histological sample may be taken.

The palpation examination of the neck area should focus particularly on the lymphatic nodes, salivary glands and the thyroid gland.

It is possible to supplement the preventive ENT check-ups referred to above by a sonographic examination, which is also relatively inexpensive, available, non-invasive and patient-friendly. The examination is capable of identifying early stages of carcinomas of the salivary glands and the thyroid gland. Furthermore, sonography can also identify enlarged or borderline lymphatic nodes.

CT or MR head and neck examinations are not suitable for identifying early carcinomas and specific laboratory tests are not available.

In conclusion, an accurate clinical examination supported by ultrasound is the only tool which can reasonably be proposed in selected groups of high risk individuals to achieve an early diagnosis of head and neck tumours.

Comment

Population screening cannot be recommended for head and neck tumours in the general population, because there is inadequate understanding of the natural history and there is insufficient evidence of the utility or cost-effectiveness. A stronger case may be made for targeting screening to head and neck cancer at-risk populations, such as smokers and heavy drinkers over the age of 40 years.

Breast cancer

Breast cancer is the most frequent cancer in females and in most Western countries represents the leading cause of death in women. In Europe, 321,000 new cases were estimated in 1995⁴⁵ accounting for 17% of deaths in women. Recent data show however a decreasing trend in mortality. Since 1990, in the USA and in some European countries such as the UK, mortality rates have fallen by 1-2% per year with a corresponding increase in survival as a result of earlier detection and improved treatment. Blanks *et al* estimate that screening may exert a direct effect reducing mortality by 6.4% (range of estimates from 5.4-11.8%) compared with the effect on mortality reduction by all other factors (improved treatment with tamoxifen and chemotherapy, and earlier presentation outside the screening programme) as 14.9% (range 12.2-14.9%)⁴⁶.

There has been much debate about the value of screening mammography.

Recently Olsen and Gotzsche⁴⁷ have contested the quality of the major trials and have concluded that there is no scientific evidence that mammography screening reduces mortality.

The update overview of the Swedish randomised controlled trials on mammography screening shows a significant 21% reduction in breast cancer mortality (RR=0.79, 95% CI 0.70-0.89). The benefit in terms of cumulative breast cancer mortality started to emerge about 4 years after randomisation and continued to increase to about 10 years. The advantageous effect of breast

screening on breast cancer mortality persists after long-term follow-up⁴⁸. The impact of screening is now under evaluation in many national and regional programmes⁴⁹. Independent work groups of the Ministry of Health of the Netherlands, of the International Agency for Research on Cancer (IARC) in Lyon and of the European Institute of Oncology and the European School of Oncology in Milan have stated that the conclusions of Olsen and Gotzsche are not scientifically based and that there is sufficient evidence that screening mammography reduces breast cancer mortality by about 35% in women of 50-69 invited to screening.

However the potential benefit of early detection of breast cancer cannot be attributed only to mammography screening in women aged 50-69, as shown by the changes in stage distribution and by the mortality decrease in women not invited to screening at younger ages.

Moreover in younger women the sensitivity of mammography is lower and in symptomatic women the benefit of integrating mammography (Mx) with other diagnostic examinations such as physical examination (PE), ultrasounds (US) and Magnetic Resonance Imaging (MRI) is well documented. Thus a comprehensive diagnosis in specific breast units should be available for all women with early symptoms or at higher risk. Although screening procedures should be based on strict cost-effectiveness criteria, in the self-referral setting women have the right of choosing more intensive protocols such as:

- to start mammography screening at an earlier age, which has been proved to be effective in single trials⁵⁰;
- to undergo palpation and ultrasounds if they were found to have a dense parenchymal pattern which is associated with high grade cancers, i.e. both a risk factor and a reason for impaired screening sensitivity^{51, 52};
- to follow a more intensive surveillance protocol if they are at high risk for hereditary cancer, although carcinogenic risks associated with radiation in these women and the benefit of early detection are not fully known⁵³;
- to undergo mammography examination every year if they are under Hormone Replacement Therapy (HRT), as a reduction in the sensitivity of screening mammography of between 7% and 21% in current HRT users has been observed⁵⁴ and the preclinical phase of cancers arising in these women, under oestrogen stimulation, may be shorter.

Women should be carefully informed of the potential benefits and adverse effects of these individual choices and the woman's individual risk should be assessed by means of standardised models⁵⁵.

A rough scheme of examinations that could be recommended to women in a comprehensive diagnostic breast unit, according to

their age and reason for presentation could be the following (Table 2).

Comment

In conclusion we believe that early detection may significantly reduce breast cancer mortality, not only by population-based mammography screening, but also by promoting self awareness and providing high quality diagnostic services. In these units, diagnostic surveillance for each woman can be tailored according to age, risk assessment, mammographic pattern and HRT use. Dedicated and trained staff, specifically trained in risk assessment and counselling, continuous monitoring of diagnostic quality, and research activities aimed at determining the most appropriate diagnostic procedures are needed.

Early aspecific cancer detection and surveillance

One of the most puzzling and intriguing of laboratory examination for cancer screening should be aspecific markers recovered from blood during routine investigation.

Many attempts have been addressed to correlate some unbalanced serum components with preclinical or hidden cancer growth: ESR, fibrinogen, orosomucoid, fibronectin, sialomucins, cytokines, etc, have been evaluated with poor predictive rates.

Actually we are focussing on free DNA plasma concentration⁵⁶, assuming that cell necrosis or apoptotic process of malignant tumours might release measurable nuclear fragments into the blood stream. Quantitative/qualitative ratios should increase the sensitivity and specificity of this method and we strongly encourage this first line investigation followed by more specific molecular genetic details chosen on the basis of the individual risk factors. Postgenomic and proteomics⁵⁷ techniques with the microarrays method are the next future trends of early cancer detection. In fact nuclear matrix proteins are strictly related to the process of gene expression. Several extraction procedures like gel electrophoresis, matrix-surface enhanced laser desorption, ionisation with direct inspection of retained proteins by time-of flight mass spectrometry, Protein Chips and tracer free biomolecular interaction are currently used to focus the diagnosis on individual types of tumours: breast and colon, prostate and bladder can be identified at an early stage but a more general screening is expected in the near future.

Discussion

According to the authors of this report, both oncologists and health authorities will have to face an increasing demand for ear-

Table 2 - Scheme of examination for the early diagnosis of breast cancer

Age (years)	Screening	Self-referral	Very high risk (>40% life-time risk)
< 40	No screening test	PE + US in symptomatic women + Mx on request	PE and US every 6 months + MRI (?) Mx starting at 35 (?)
40-49	Screening (Mx every 12-18 months) according to Local Health Unit policy	Mx every 12-18 months + PE and US in symptomatic women	Mx every 12 months + PE and US every 6 months + MRI (?)
50-69	Mx every 24 months	Mx every 24 months (every 12 months in HRT users)+ PE and US in dense breasts(?)	Mx every 12 months + PE and US every 6 months

ly detection of cancer as a consequence of the awareness campaigns launched nearly everywhere (and certainly in Europe) by governments and cancer charities. People have now learned to cope with the idea that they can develop cancer but do not want to die from it, particularly because of delayed diagnosis: as a matter of fact the advance in genetic decodification is opening new perspectives of microarrays and proteomics techniques of cancer detection, on large population cohorts. But we have to come back to the day by day early tumours detection policy, where the state-of-the-art still leaves much to be improved in terms of evidence-based medical protocols.

In the meanwhile, preclinical research on applied genetics is supposed will supply us with very accurate weapons for prevention and diagnosis, but it will take some years of clinical investigations before that these epidemiological screenings will be part of a widespread panel of social health and welfare programming. On the other hand we do have still unresolved basic questions on this practice; for instance, who is in charge of early detection of cancer? The published data report that single Institutions (hospitals, or Universities) but also public and occupational medicine have taken the challenge for specific high risk population targets; generally speaking governments are quite reluctant to support large cancer campaigns because of the heavy cost, the very complex organization network, and the preliminary need for capillary information for the citizen.

One more question is: where can doctors and nurses “learn” early detection? We strongly believe that a formal programme in the main oncology schools, like the ESO, should be part of qualification and continuing medical education. This specific subject should enclose materials, methods and strategies for early detection in order to create in each cancer Institute or Hospital, a Registry dedicated not only to prevention but also to early diagnosis of tumours. Trained and qualified oncologists should in turn teach at CME conferences of family physicians and nurses, either to create a first step screen in their office, or to stimulate adequate follow-up and compliance of their patients with institutional trials.

The way of early detection is then open to new challenges: while waiting for definite genetic tests we ought to amplify the user network, and to improve the tools for easy and standardized screening.

Acknowledgements

This study was supported by Lega Italiana per la Lotta Contro i Tumori, Rome – Italy. We wish to thank Mr. William Russell-Edu, librarian at the European Institute of Oncology, Milan, for his collaboration.

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