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Addressing overdiagnosis and overtreatment in cancer: a prescription for change

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Abstract

A vast range of disorders—from indolent to fast-growing lesions—are labelled as cancer. Therefore, we believe that several changes should be made to the approach to cancer screening and care, such as use of new terminology for indolent and precancerous disorders. We propose the term indolent lesion of epithelial origin, or IDLE, for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated. Furthermore, precursors of cancer or high-risk disorders should not have the term cancer in them. The rationale for this change in approach is that indolent lesions with low malignant potential are common, and screening brings indolent lesions and their precursors to clinical attention, which leads to overdiagnosis and, if unrecognised, possible overtreatment. To minimise that potential, new strategies should be adopted to better define and manage IDLEs. Screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with

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the same energy traditionally used to increase the sensitivity of screening tests. Changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medicolegal notions and perceived risk to reflect the evolving understanding of biology, be more judicious about when a biopsy should be done, and organise studies and registries that offer observation or less invasive approaches for indolent disease. Emphasis on avoidance of harm while assuring benefit will improve screening and treatment of patients and will be equally effective in the prevention of death from cancer.

Introduction

On March 8–9, 2012, the National Cancer Institute convened a meeting to assess the problem of cancer overdiagnosis, which occurs when tumours that would otherwise not become symptomatic are identified and treated. When this overdiagnosis is not recognised, it can lead to overtreatment. Participants of the meeting agreed that with the deployment of increasingly sensitive imaging tests, more lesions are being identified and labelled as cancer. This Personal View describes the initial steps to address the increasing problem of overdiagnosis and overtreatment.

The word cancer encompasses a range of disorders, from those that are always lethal if left untreated (or even if treated) to indolent lesions with extremely low potential for metastatic progression and death.[1] Several other diseases show a similar range of severity—eg, diabetes can progress slowly or rapidly, as can rheumatoid arthritis, hepatitis, coronary artery disease, and inflammatory bowel disease. Unfortunately, when patients hear the word cancer, most assume they have a disease that will progress, metastasise, and cause death. Many physicians think so as well, and act or advise their patients accordingly. However, since many tumours do not have the unrelenting capacity for progression and death, new guidance is needed to describe and label the heterogeneous diseases currently referred to as cancer.

Benefits of screening, according to cancer type

Screening is based on the assumption that cancer has an orderly and gradual progression (figure 1A). Good survival outcomes for patients with the earliest stages of disease led to the conclusion that detection of cancer at an early stage would dramatically reduce cancer mortality. For some cancers, incidence of disease dropped after screening was initiated (eg, cervical and colon cancer), but it increased for others (eg, breast and prostate cancer).[1] In breast and prostate cancer, for example, screening has not had as big an effect on mortality, or elimination of regional (stage II or III) disease, as was expected,[2] which begs the question: why not, and what can we do to improve this situation?

Molecular dissection of the genome has clearly shown cancer heterogeneity between and within organ sites and within tumours.[2–8] A model of cancer progression that is more suited to the current understanding of cancer biology is one of variable progression, depending on stromal or tumour type, that includes indolent lesions and those that disseminate either early or late (figure 1B). The types (eg, indolent, aggressive) of tumours that develop and their prevalence in the population, coupled with the availability of effective therapy and the

ability of early detection to avoid extensive treatment, affect whether the net effect of screening will be harmful, neutral, or helpful in the reduction of morbidity and mortality (figure 1B).

If a tumour develops slowly but is likely to progress if unchecked, early detection is most likely to be beneficial. For instance, removal of cervical intraepithelial neoplasia reduces incidence of cervical cancer, and removal of adenomatous polyps during colonoscopy reduces the incidence of colon cancer. Note that neither are called cancer.[9] The optimal screening frequency for cervical cancer is 3 years, and for colon cancer generally 5–10 years. For tumours that develop rapidly or disseminate early, screening is much less likely to improve outcomes. The ability to identify individuals at highest risk for these lethal and rapidly growing cancers has led to more frequent screening (as is the case for breast cancer screening for carriers of *BRCA1* and *BRCA2* mutations). In patients at high risk for extremely aggressive (*BRCA1*) breast cancers, prevention strategies (eg, prophylactic surgery) are life saving compared with screening, and the development of more effective treatment strategies is a high priority.[10]

In patients in whom the detected disease is indolent (eg, those with prostate cancer with a Gleason score of 3+3 or lower), screening will probably have no health benefit;[11] if treatment-related morbidities occur, the net effect of screening is harmful. If treatment and outcome are the same irrespective of whether the tumour is 1 cm or 3 cm at detection, then no net gain will be achieved.

Indolent tumours either stop growing or grow very slowly. Such tumours are often reported in high numbers in autopsy studies, because people usually die with them, not of them.[12] Some tumours even regress, the best example of which is neuroblastoma. Historically, screening for neuroblastoma was initiated because this childhood cancer could be detected by urine catecholamines, and seemed to have a better prognosis if diagnosed before the age of 1 year. However, results of a large screening programme (476 694 children) in Quebec, Canada, showed that screening was not effective—in fact it was harmful.[13] The proportion of lethal cases did not decrease, nor did mortality, but many more cases of what is now called neuroblastoma S (the spontaneously regressing type) were detected and treated with surgery and chemotherapy. This spontaneously regressing form had not previously been recognised because, until screening, these tumours rarely came to clinical attention.[13] This example draws attention to two important principles: tumours can regress, and treatment of indolent tumours can often cause harm.

More is being discovered about the complex factors that contribute to malignant or indolent growth (figure 2A). Cancer behaviour is strongly affected by signalling pathways and the microenvironment or organ in which it arises, determining fate, rate of progression, and response to therapeutic interventions.[14,15] In this highly variable environment, biology is likely to have more of an effect on outcome than tumour stage. For example, a small tumour can have a high metastatic potential, whereas a large tumour can have low metastatic potential. An understanding of these additional biological factors will improve strategies for prevention and screening. This improvement in strategy is a challenge and opportunity for the scientific and clinical community, and is particularly urgent because the median age of

the US population is rising, with a third expected to receive a cancer diagnosis during their lifetime.

Screening and detection of indolent tumours

The concept of the IDLE lesion

Screening undoubtedly detects indolent disease, best exemplified in prostate cancer,[16,17] breast cancer,[1] and even lung cancer.[18–20] This detection of indolent disease is mainly due to the inherent tendency of all screening tests to preferentially detect slower growing cancers because more rapidly growing cancers are more likely to present between screens. Indolent disease might account for 15–75% of all cancers, depending on organ type.[8] Disease-based screening and diagnostic scans for various purposes have contributed to cancer overdiagnosis, which leads to overtreatment when not recognised, thus reducing the overall effectiveness of screening.[9] The increased detection of indolent lesions has led us to propose use of the term indolent lesion of epithelial origin, or IDLE, instead of cancer, when a subset of disease can be determined to have an extremely low risk for metastatic spread. For some tumour types, this differentiation is now possible to make. For others, more work will be needed to develop and validate markers for an IDLE classification. The IDLE classification would probably make care providers and their patients more willing to participate in trials or registries of less aggressive interventions.

Thyroid cancer

Thyroid carcinoma is an excellent example of how technological advances in diagnostic imaging have led to the detection of a reservoir of indolent disease. Between 1975 and 2009, the incidence of thyroid cancer nearly tripled in the USA (from 4·9 per 100 000 to 14·3 per 100 000), whereas the death rate remained constant (from 0·56 per 100 000 to 0·52 per 100 000).[21] The increase in incidence has been almost entirely due to small (<2 cm) papillary cancers, the most indolent histological type.[22] Results of a study of Finnish adults showed that 36% of participants without any previous history of thyroid disease had at least one papillary carcinoma at autopsy.[23] The rapid growth of ultrasound and fine-needle aspiration in the mid-1980s probably increased detection.[22] Although only 4–7% of the adult US population has a palpable thyroid nodule, about 50% have a thyroid nodule detectable by ultrasound.[24] One thoughtful radiologist has questioned whether it is “time to turn off the ultrasound machines” because the impalpable cancers detected by ultrasound are almost uniformly indolent.[25] If these lesions with excellent prognosis were reclassified as IDLE disorders, the need for aggressive therapy and screening would be mitigated.

Prostate cancer

Adenocarcinoma of the prostate is probably the tumour with the greatest risk for overdiagnosis and overtreatment. During autopsy, tumours are often detected in the prostate, with older men more likely to have an indolent tumour (ie, a man aged 60 years might have a 50–60% risk of occult cancer).[12] With repeated prostate-specific antigen (PSA) testing and 10–12-core biopsy of the prostate, often done repeatedly, small, low-grade tumours are frequently detected.[26] Attesting to the relatively low biological potential of these lesions are the 99% and 97% disease-specific survivals at 5 years and 10 years of follow-up,

respectively, for men who are simply monitored and only given treatment if they have evidence of a grade or volume increase.[11] Despite this indolent behaviour, greater than 90% of these tumours are treated with radiation or surgery,[27] generating morbidities of treatment (eg, sexual, urinary, and gastrointestinal side-effects, in about 15–20% of patients), increased risk of secondary malignancies (with radiation), and increased cost.[28] Even active surveillance is hampered by the growing risk of sepsis in men undergoing repeated biopsies accompanied by increased cost and anxiety.[29] New diagnostic methods and reclassification of low-risk lesions as IDLEs would reduce morbidity. Other potential approaches to improve screening include screening on the basis of risk, or the combination of PSA testing and chemoprevention with finasteride, to reduce the risk of detection (and treatment) of indolent tumours.[30]

Lung cancer

Carcinoma of the lung is the leading cause of cancer-related death in the world. At diagnosis, 70% of patients have locally advanced (stage III) or metastatic (stage IV) tumours, for which less than 10% of patients survive for 5 years.[21] However, 70% of patients with stage I disease survive for 5 years, and 40% of those with stage II cancers. This finding has prompted major efforts to develop early detection programmes. However, lung cancer screening studies and autopsy reports[31,32] suggest that a substantial subset of screening-detected cancers are indolent, even in the setting of a cancer type often thought to be aggressive, with 20–25% of cancer detected estimated to be overdiagnosed.[8,33]

The National Lung Screening Trial[34] reported a 20% relative reduction in lung cancer death with low-dose helical CT (LDCT) screening compared with chest radiograph; however, this finding was seen only in high-risk populations assessed at institutions with cancer expertise.[34] Furthermore, the increase in early-stage disease was substantially greater than the reduction in more advanced cancers[20] and results of an analysis suggest that the probability of overdiagnosis for any lung cancer is 18·5% (95% CI 5·4–30·6) with LDCT, varying on the basis of subtype.[35] Importantly, in the LDCT group, 39% had at least one positive screen, of which 96% were false positives. Nodules under 1 cm in diameter had only a 1·5% chance of being cancer. Thus, the US Preventive Services Task Force concluded that the balance of benefits versus harms of LDCT screening justified screening, but only for the highest risk populations at experienced centres; and recommended that patients be informed of benefits and harms (including complications of diagnostic procedures, radiation exposure, and effect on quality of life) of identification of low-risk lesions.[20,36] Development of diagnostic tests to distinguish between indolent (IDLE) and aggressive tumours will mitigate overtreatment.[37]

Invasive breast cancer

Since 1983, the incidence of invasive breast cancer has risen substantially, especially the incidence of cancers with less aggressive characteristics.[1,38] Although overdiagnosis of indolent lesions has been recognised to be a result of screening,[39] the extent is under-appreciated.[40] Of screening-detected invasive breast cancers, up to 30% might be ultra-low risk on the basis of their molecular profile.[40] If validated, this proportion of low-risk cancers presents an opportunity for an IDLE classification.[1] Molecular classifiers are used to avoid

chemotherapy,[41,42] but could also classify tumours that have a very low or no risk of metastatic progression after simple excision, supporting the safe elimination of radiation therapy after lumpectomy in postmenopausal women, benefiting many women.[43–45]

Strategies to reduce overdiagnosis include changing thresholds for when to undertake a biopsy, reducing the frequency of screening, focusing attention on elimination of consequential tumours, and developing more risk-based screening approaches.[46] Most lesions recommended for biopsy are benign. If low-grade and intermediate-grade ductal carcinoma in situ were not a focus of screening, far fewer biopsies would be done.[46] Screening every other year as recommended by the US Preventive Services Task Force, and most countries outside the USA, would lower the number of false-positive biopsies, without increasing the risk of late-stage cancers.[47] Concentration of screening in high-volume mammography centres, which have access to tests with better sensitivity and specificity, will further improve the process.[48] Risk-based screening should be developed, and recommendations should be based on the type of breast cancer for which women are at risk.[47–50] Over time, people might be identified for whom little or no screening is the best strategy, as has been shown in lung cancer.[20]

Non-melanotic skin cancers and melanomas

About 2·2 million predominantly older (>65 years) Americans are diagnosed with non-melanoma skin cancers every year, including basal-cell and squamous-cell cancers.[51] The number diagnosed and given aggressive treatment has risen by more than 50% in the past decade.[52,53] Except in some small, immunosuppressed populations, basal-cell and squamous-cell carcinoma are rarely fatal. If left untreated (for years), they can cause local problems, some serious. Despite less invasive treatment options being available, the proportion of aggressive surgical procedures done in patients with limited life expectancy is almost the same as in healthy individuals.[51] Non-melanotic skin cancer is a candidate for change in terminology to promote safe alternatives to large excision or Mohs' surgery, such as observation.

Melanoma diagnoses have increased worldwide, but the rise is predominantly due to stage I melanoma diagnoses, without a drop in mortality. This increase has been ascribed to a rising proportion of patients undergoing biopsy, and to stage-drift (ie, a shift over time in how types of lesions are defined; for example, tumours once considered to be in situ might now be defined as stage I).[54,55] Melanoma, however, is an important disorder and can be lethal. Incidence and mortality have increased, despite a huge increase in the excision of benign skin lesions.[9,56] The challenge for the community is to establish what will reduce the incidence of consequential cancers and their attendant mortality. Resources and efforts should be focused strategically.

Precancerous lesions

All screening can lead to the identification of lesions that are not consequential—especially in the case of precancerous lesions, which are far more abundant than their invasive counterparts. Screening programmes that have evolved to target precancerous lesions are successful if removal of the precancerous lesions causes minimal morbidity or psychological

harm, and if removal of these lesions results in a decrease in invasive cancers. This strategy has been more successful in some cancers (eg, colon and cervical) but not others (eg, breast cancer, Barrett's oesophagus). However, many more colon polyps and cervical neoplastic lesions are removed than would progress to colon cancer or cervical cancer.[38,49,50] In both cases, screening frequency has been safely reduced to decrease screening burden and potentially unnecessary interventions. Importantly, polyps and cervical neoplasia are not called cancer. Terminology for other precancerous lesions should change to reduce urgency of intervention and enable assessment of new strategies for screening and treatment.

Fuelled by fear of missing the chance for early detection, an aggressive strategy of undertaking biopsies has evolved. When radiologists recommend a biopsy, primary care physicians and oncologists feel compelled to follow the recommendations, unaware that many of these target lesions are benign or indolent, and behave as if the philosophy to leave no stone unturned causes no harm. However, the result is that biopsy samples are taken from hundreds of thousands of benign lesions, and treatment is given for tens of thousands of precancerous lesions that, if left alone, would never be lethal. In addition to needless morbidity, these interventions cost billions of dollars.[57]

Barrett's oesophagus

One school of thought is that Barrett's oesophagus is a precancerous disorder arising as a complication of chronic reflux that greatly predisposes to oesophageal adenocarcinoma. The route to reduction of mortality caused by oesophageal adenocarcinoma seemed to be to screen patients with reflux symptoms, enrol those with Barrett's oesophagus in long-term surveillance, and give them aggressive, invasive treatments such as endoscopic ablation. However, evidence shows that Barrett's oesophagus is typically a homoeostatic adaptation to the reflux environment and that most individuals with it will neither develop nor die of oesophageal adenocarcinoma.[58] Routine screening of individuals with reflux to detect Barrett's oesophagus is no longer recommended by major gastrointestinal professional societies.[59–61] Evidence is in short supply to show clinical benefit from endoscopic screening for Barrett's oesophagus, yet this practice continues. Terms such as precancer and premalignant cause undue fear in patients and clinicians and lead to overly aggressive interventions. A more accurate and descriptive, IDLE-like term is intestinal metaplasia, and should be used instead, with a notation of dysplasia grade or depth of penetration.

Ductal carcinoma in situ

Ductal carcinoma in situ is a pathological entity that is an unintended result of breast cancer screening, rarely diagnosed before screening was adopted. Diagnosis of ductal carcinoma in situ results in immediate treatment with aggressive locoregional therapy; however, the natural history of untreated ductal carcinoma in situ has never been elucidated.[62] Results of studies suggest that only a subset of ductal carcinoma in situ progresses to clinically significant invasive cancer during a patient's lifetime.[63] The result of this historically aggressive treatment approach is that nearly 50 000 women per year in the USA are diagnosed and given treatment, 20 000 of whom undergo mastectomy, with a growing proportion opting for bilateral mastectomy.[64,65] Yet incidence of invasive cancer has not dropped concomitantly. Emerging molecular markers have identified a group of patients

with ductal carcinoma in situ whose risk for developing breast cancer is not much higher at 5 years than that of an average woman aged 65 years (2·5%).[66,67] Registries and trials that explore surveillance as an alternative to surgical treatment, using imaging and tumour markers, such as the CALGB trial 40903 (NCT01439711), will hopefully change how ductal carcinoma in situ is managed. Lesions in this disorder range from low to high grade. The lowest-grade ductal carcinoma in situ lesions behave more like atypia, with risks for invasive cancer at 10 years in patients with low-grade lesions similar to risks in patients diagnosed with atypia.[61] Removal of the word carcinoma from the diagnosis of low-grade lesions, and use of an IDLE term such as atypical lesion, will encourge adoption of new approaches.[68]

Atypical naevi

Thousands of atypical naevi are excised every year, but little to no evidence exists to show that any dysplastic naevi evolve into melanoma. When dermatologists self-refer pathology, their biopsy rates increase by 30% per year.[69] Solutions include reassessment of precursor lesions (eg, dysplastic naevi) for their consequential cancer potential and the use of computer-aided diagnostic methods to set better thresholds for biopsy.[70] Efforts have been made to establish an expert panel to identify solutions (including changes in terminology) to reduce benign biopsy rates and overly aggressive procedures.[8,9]

The challenge of changing screening practice

These examples show the weaknesses of screening and how screening might lead to net harm while seeming to do good. An inflated perception of the benefit of screening and early detection (figure 3) leads to public confusion when problems with screening surface. The belief in benefits of screening is so pervasive that it prompts recommendations to screen even when consensus is that a test is not of value, as in ovarian cancer.[71] In the face of complicated evidence, physicians and patients alike make decisions in an environment in which aggressive behaviour is promoted—the decision to screen, and then to treat aggressively if something is discovered—even if the net effect is unintentionally negative.[72] Fear of committing malpractice by not doing enough, the assumption that any disease called cancer will lead to death, and the ingrained cultural response to fight cancer all cloud the ability to recognise when screening or early diagnosis might be creating a problem. No negative feedback loop exists. Inadvertent harm can occur through anxiety, fear of recurrence (when recurrence is extremely unlikely), or unintended overtreatment and subsequent side-effects. Strategies to minimise that harm need to be rethought and redeveloped. Treatments are evolving to become more targeted as new molecular tests help to stratify disease subtype and outcome. Screening can no longer be approached as if cancer were a uniform disease; public policy should evolve as new knowledge is gained if public health benefits are to be realised.

A call for change

We attended the March 8–9, 2012, US National Cancer Institute multidisciplinary brainstorming meeting and agreed that it was important for the medical community to recognise that cancer overdiagnosis is an increasingly common problem. We, along with the

other participants, made the following recommendations for consideration and dissemination (summarised in panel).

Change cancer terminology

The first recommendation was to change cancer terminology—ie, decrease use of the word cancer when it is not appropriate and increase use of the term IDLE. The word cancer should be removed from the names of lesions thought to have a very low likelihood of progression and be replaced with the term IDLE. Currently, pathological descriptions and labels are based on appearance and are a static snapshot of a lesion.[72] Instead, the basis of labelling a lesion as cancer should be its behaviour or outcome.

There is a clear precedent for changing the names of tumours to reflect increasing knowledge about benign disease behaviour to provide useful and reassuring guidance to clinicians and patients. In 1998, the WHO classification of urothelial tumours was revised, reclassifying papilloma and grade 1 carcinoma as papillary urothelial neoplasia of low malignant potential, taking the lowest grades of tumour and removing the word carcinoma.[73] The reasoning behind the change was that a disorder that is almost never associated with invasion and disease progression should not be called a carcinoma at all.[73] Similarly, designation of cervical intraepithelial neoplasia as a low-grade lesion, not a malignancy, has resulted in a substantial decrease in procedures and a switch to observation for patients with this disorder, without a concomitant increase in cancer diagnoses.

Panel: Consensus of the working group recommendations regarding overdiagnosis and overtreatment presented to the National Cancer Institute

1. Recognise that overdiagnosis occurs and is common
2. Embrace the development of new terminology to replace the word cancer when appropriate, when data or companion diagnostics support the classification of low-risk lesions as indolent lesions of epithelial origin (IDLEs)
3. Create observational registries for IDLEs and disorders with low or uncertain risk of progression to cancer
4. Mitigate overdiagnosis by testing strategies that lower the chance of detecting unimportant lesions
5. Embrace new concepts for how to approach cancer progression and prevention

The words used to describe a disorder substantially affect choice of intervention.[74] Thus, precancerous lesions that confer low risk for development of a malignant disorder or lesions that have low risk for development of metastatic disease should not include the term cancer (figure 2B). Biomarkers, pathological analyses, and epidemiological studies should focus on the identification of lesions that confer a low risk and are more suited to terms such as IDLE, which more clearly communicates the lack of risk associated with such lesions.[1] What defines low risk needs to be worked out on the basis of the likelihood and effects of recurrence, and will vary by organ site. Companion diagnostics should be developed to

support doing less safely—providing reassurance to clinicians and patients—and enable changes in behaviour.[41,42]

A multidisciplinary effort across the pathology, imaging, surgical, advocate, and medical communities should be convened by an independent group such as the Institute of Medicine to revise the terminology framework and taxonomy of lesions currently called cancer, and create classification criteria for IDLE disorders.[75] Once established, these definitions could be updated according to new data.

Create observational registries for lesions

Additionally, the creation of observational registries for lesions with low malignant potential is recommended. Provision of information for patients, not just about their diagnosis, but also about the dynamics of their disease, is essential for making informed treatment decisions that include strategies such as active surveillance. For precancerous lesions, surveillance should be about prediction of the development of an invasive cancer, as well as the time period during which that risk might occur (eg, 1 year *vs* 10 years) and the type of invasive cancer that might develop.

Two important methods to refine optimal treatment strategies are time and behaviour in the face of therapeutic pressure. For slow-growing, low-risk lesions, time can be used to establish when an intervention is needed.[16,17] For example, pulmonary nodules too small to characterise, detected on screening CT examinations, are usually followed up by one more CT and then dismissed as benign. A timeframe during which treatment and prevention could occur before excision might be useful to develop alternative treatments and preventive indicators.[76]

Registries of watchful waiting or prevention and less aggressive interventions should be regarded as safe and an emerging standard of care, without the need for aggressive repeated biopsies, even as more is understood about the natural history of cancers. We call upon the medical community to encourage appropriate participation in such registries, because of the potentially enormous benefit to patients and society. Data should be captured in a consistent and standardised manner to promote actionable changes in treatment. Harm in this setting is exceedingly unlikely and far less than the harm of continuing to intervene uniformly when, for most patients, treatment is unnecessary and provides little or no real benefit.

The task is to begin to define those groups of low-risk disorders for which observation and change over time will help to define the benefit of intervention.[58,77] One of the patient advocates who took part in the meeting recommended that a descriptive term or test or an analytical method (eg, growth rate evaluation and analysis technique test) is developed and standardised to establish the appropriateness of surveillance alone and inclusion in registries. A test that implies it is safe to observe would be less anxiety-provoking than terms such as watchful waiting.

Mitigate overdiagnosis

Strategies to lower chances of indolent disease detection include: avoidance of diagnostic assessments that are not truly necessary; reduction in the frequency of screening

examinations; screening of the segment of the population that is at highest risk; and raising of the threshold for recall and biopsy. Work-flow strategies to look for clinically significant disease, such as the addition of multiparametric MRI after raised PSA is detected, can reduce the number of biopsies.[78] Learning when not to take a biopsy sample is more cost effective, however, than the addition of another expensive test. The Prostate Cancer Risk Calculator is an example of a method that patients and physicians can use to assess their risk for low-grade (IDLE) versus high-grade tumours.[79] If higher thresholds for risk of invasive cancer are set before a biopsy is recommended, the chance of finding inconsequential disease in both breast and lung cancer screening would be reduced. Avoidance of routine screening for some cancers for which the evidence of overdiagnosis is strong and level 1 and 2 evidence for screening benefit is absent (eg, for thyroid cancer) would be the best way to avoid overdiagnosis altogether.[9] Strategies to raise the biopsy threshold can be safely studied by recognising that, for many IDLE disorders, delay in diagnosis is unlikely to affect disease outcomes.[46] Finally, for lesions of low malignant potential, radiologists should avoid giving specific clinical instructions, such as biopsy recommendations, that make observation of the behaviour of these lesions over time more difficult. These strategies will reduce the distress caused by excessive scrutiny.[80]

Search strategy and selection criteria

We identified references for this Personal View by searching PubMed with the search terms “over diagnosis”, “over treatment”, and “cancer”. We looked at articles published in English between Jan 1, 1985, and the date of our last search (Nov 25, 2013). We also used and shared our extensive databases, and individual authors were assigned to review each organ subtype discussed in this Personal View. There were more references than could be accommodated by the manuscript reference limit, so the most seminal and relevant articles were selected for final inclusion in the reference list.

Expand our concept of how to approach cancer progression

Lastly, we recommended that our concept of how to approach cancer progression should be expanded. Emerging models suggest that tumour micro environment might be as or even more important than genetics of the tumour itself. Factors that prevent the transition of precancerous to cancerous lesions include the host’s genetic susceptibility and the permissiveness of the organ microenvironment.[81] New models for prevention of progression could focus on approaching cancer in a similar way to how the maintenance of an ecosystem is approached.[14,81] The stroma or micro environment might be an excellent target for prevention of metastasis and could be an alternative to the current approach of removal of any malignant or premalignant cells.

Conclusion

In conclusion, we have discussed the harms that are accruing from a one-size-fits-all approach to cancer screening and overuse of the term cancer. To reduce the substantial harm from this approach and to reduce the overall burden of cancer, the wide range of behaviours and outcomes associated with what is currently called cancer should be recognised. As a

collective community of clinicians, researchers, patients, and stakeholders, the challenge is to redefine cancer based on its behaviour, use terms such as IDLE when appropriate, and change communication methods. The approach to cancer screening and treatment can then be tailored accordingly to maximise benefit to the individual patient and the population.

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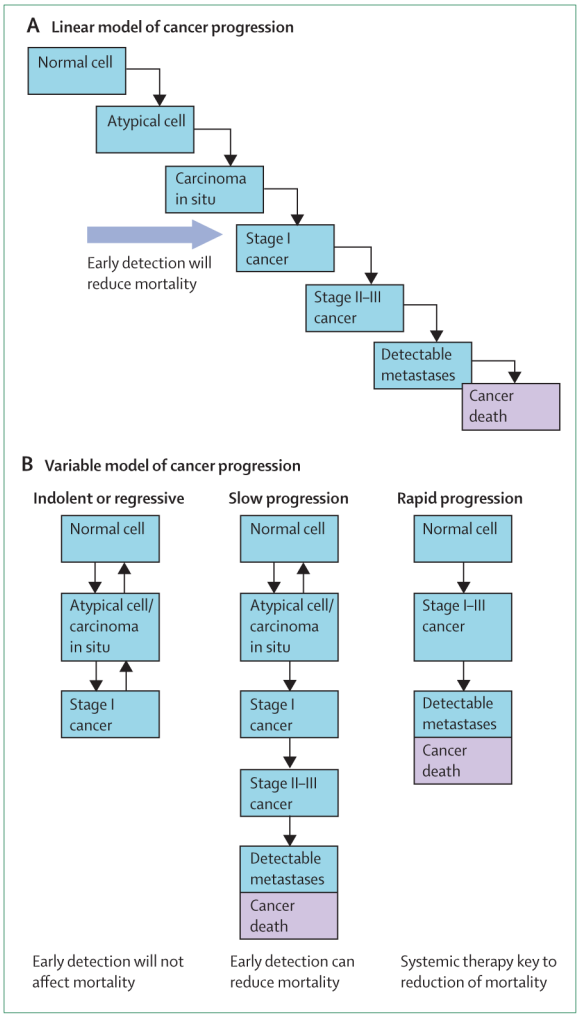

Figure 1. Models of tumour progression can affect screening benefit

(A) A linear model of tumour progression presumes that cancer progresses from early events (atypia or in-situ disease) to late-stage or metastatic disease and death, and that early detection is crucial to reduce mortality. (B) A variable model presumes that cancer can have variable progression on the basis of biology and that the range of disorders spans from indolent to slowly or rapidly progressive. Screening might lead to overtreatment and harm, benefit, or have a minimal effect, respectively.

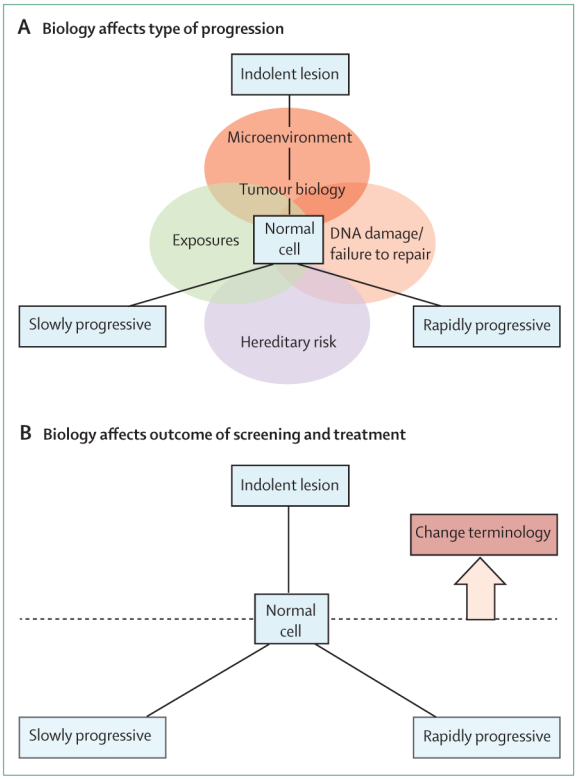

Figure 2. Biology affects tumour type, behaviour, and effect of screening and treatment

(A) Tumours that develop are controlled by several biological variables, and are the result of complex interactions among tumour subtypes, their microenvironment, and other factors shown here—eg, exposures to things in the environment that can cause cancer. (B) Tumour type and behaviour affects screening outcomes; the term indolent lesion of epithelial origin, or IDLE, can be used for indolent tumours if they can be identified at diagnosis or after a period of observation.

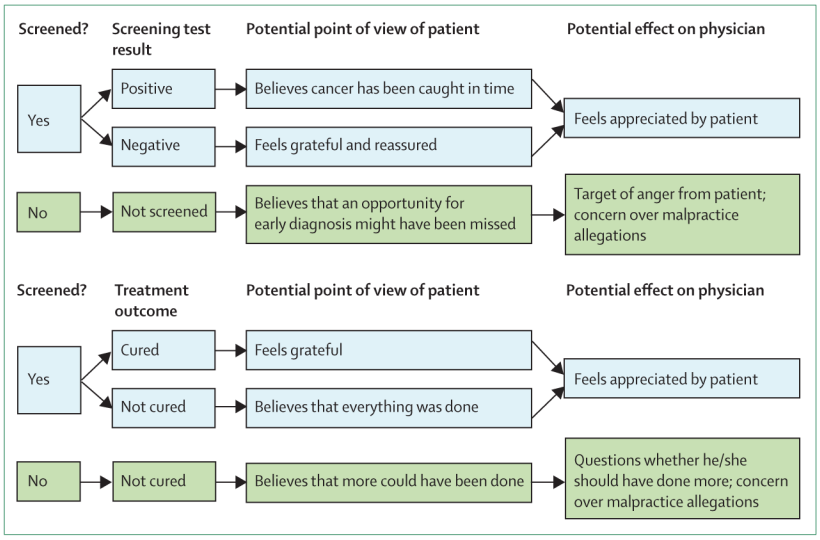

Figure 3. Factors that can reinforce decisions for aggressive screening and treatment

In the face of complicated evidence, physicians and patients make decisions in an environment in which intervention and aggressive behaviour is rewarded. The potential beliefs and effects shown here are for prostate cancer screening.[72]