Cancer Prevention II

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Abstract Finding the optimal use of health-care resources requires the reliable estimation of costs and consequences. Acquiring these estimates may not be difficult for some common treatments. More difficult is the optimization of resources in the area of diagnostics. Only a few attempts have been made to optimize the use of resources in the area of prevention. Several aspects have to be considered when optimizing the resources for prevention: (1) participation rates in structured prevention programs are low, (2), acquiring data on follow-up and outcomes is difficult, (3) there are concerns about the quality of information available to public, and (4), the public is often unaware of scientific assessments of prevention programs. As prevention programs are costly long-term projects, a strategy to select these programs according to possible predictors of success might be useful. The few analyses of cancer prevention in the literature have been directed towards the most common malignant diseases (as assessed by incidence) such as cancer of the breast, colon, lung and prostate. We argue that incidence is a poor marker for selecting secondary prevention programs. Incidence may be a misleading indicator for two reasons: incidence of disease does not predict efficiency of management or good health outcomes, and incidence does not separate clinically significant from non-significant disease. The traditional strategy is based on the assumption that more screening increases the chance of cure. We propose an alternative outcomes model that suggests better disease management justifies new prevention programs. Indicators for better disease management are effective and efficient treatments as well as high-quality screening (sensitivity and specificity) techniques and possibly “side-effects of prevention programs,” which provide early signs of success to motivate the patient’s participation, to keep up with the program and finally to succeed.

2.1 Introduction
Optimal use of health-care resources presumes the reliable estimation of the costs and the consequences of health-care services. These estimates are available for many treatments. More difficult is the optimization of resources in the area of diagnosis and prevention where these estimates are rare. Optimizing the resources for prevention requires consideration of several issues: first, the difficulty in acquiring follow-up and outcome
data; second, the assessment of value of prevention programs from a scientific point of view; third, concerns about true information of the public and assessment of the value from the view of the public; and finally, the assessment of value of prevention programs by individual persons resulting in the participation rates in structured prevention programs. These aspects make it difficult to select the optimal among several possible prevention programs. The saying “an ounce of prevention is worth a pound of cure” may be not true (Gérvas Camacho et al. 2007; Sackett 2002; Schwartz et al. 2004; Welch 2004) unless there is some supporting evidence.

Most fields in health care require evidence before a new strategy is adapted for routine clinical practice. In preventive medicine the generation of such data is difficult for two reasons. Large and long-running studies have to confirm the successful prevention of the target problem, which is usually many years into the future. Long-term effects may attract less attention than immediate effects. In addition, professionals and patients tend to invest less energy to reach distant benefits unless there are early indicators which confirm that the intended long-term benefit will be achieved. Second, unlike in clinical trials on new treatments, it is not possible in prevention studies to start with a small pilot study followed by the main study because of the required long study periods. These decisions, which have to be made before initiation of a prevention program, will be easier if predictors of successful prevention programs can be identified. The identification of such predictors is the aim of this paper.

2.2 Methods

We performed a literature search on established and recommended programs to screen for and prevent malignant diseases in Europe and the United States. In order to assess the quality of prevention programs we looked for the markers’ “structure” and “process”. In addition we searched for data on effectiveness of prevention programs. Finally we tried to find selection criteria for preventive programs.

2.3 Results

2.3.1 Quality of Prevention Programs

2.3.1.1 Low Participation Rate in Structured Prevention Programs

The Zentralinstitut, the central institute of the major public health insurer in Germany, analysed 506,500 cases of colonoscopy screening data in addition to information from 544,000 colonoscopies performed over 3 years (Zentralinstitut 2007). The acceptance rate in those aged up to 74 years was 8.8% for men and 10.2% for women.

2.3.1.2 Difficulty in Acquiring Follow-Up and Outcome Data

The acquisition of follow-up and outcome data is often a problem in prevention studies. After about 18 months, both the trial staff and the members of the target groups lose interest in participation. Yet an 18-month observation period is insufficient for primary or secondary prevention studies. For this reason, the loss of interest and attention might be prevented if predictive indicators of late effects can be found.

2.3.1.3 Concerns About Correct Perception of Scientific Information by the Public

There is strong evidence that the public support screening programs (Schwartz et al. 2004). The propagation and measurement of tumour mark-
ers in blood samples was widely recommended in the 1970s and 1980s and was well accepted by the patients. Increasing scientific evidence and the corresponding publications (Hayes 1996; Jacobs and Haskell 1991) have led to a considerable reduction in their use as screening tool. This reduction was difficult to achieve because doctors as well as their patients had received different information in the years before. Scientists had published the advantages of tumour marker screening and practicing doctors as well as patients were consequently convinced of the predictive value of tumour markers and the need to include them in follow-up programs.

There is typically more enthusiasm for screening when no or only little harm of the screening is perceived by the target groups. This is true for blood tests and for mammography screening but only to a lesser extent for procedures which patients find more harmful or unpleasant such as endoscopies and biopsies. For a more detailed discussion the scientific information on secondary prevention will be presented for colon and breast cancer.

2.3.1.3.1
Effectiveness Using the Example of Screening for Breast Cancer
A review of the Cochrane collaboration on breast cancer screening (Goetzsche and Nielsen 2006) pointed out that 2,000 women of the age group 50–69 years have to be screened to prevent one additional death from breast cancer. There is general agreement on a small but true benefit from breast cancer screening although the estimates vary among authors. This gain in life-years has to be compared with three disadvantages associated with screening for breast cancer. First, about 30% of the expected breast cancer cases will have a false-negative screening result (clinically detected cancer following a negative screening result). Second, about one-fifth of all screening tests will produce a false-positive result and will cause anxiety, concerns and costs of additional tests (Elmore et al. 1998). Third, in 10 of these 2,000 women, screening will lead to the diagnosis of breast cancer (and subsequent treatment) that would have neither influenced the life expectancy nor the quality of life of the patient if the cancer had not been detected by mammography. We use the term pseudodisease to describe identifiable pathology that has no clinical importance in terms of life expectancy or quality of life (Kaplan 2006; Shorter 1997; Woolf 2003). Pseudodisease has been discussed in relation to oncology but is also referenced in cardiovascular disease (Black and Czum 2007) and hypothyroidism (Woolf 2003). Patients have difficulty understanding this information because we do not know which individuals with positive results will develop clinical disease. At best, we can only offer proportions in the populations. In the case of breast cancer, we have to treat all women with a confirmed diagnosis although we know that 20%–30% of these patients will not benefit from the treatment they receive (Goetzsche and Nielsen 2006; Barrat et al. 2005).

2.3.1.3.2
Effectiveness Using the Example of Screening for Colon Cancer
Early studies (Mandel et al. 1993) reported in 1993 that a 33% reduction in the 13-year cumulative mortality can be achieved by faecal occult blood testing (FOBT). The study randomized over 45,000 adults to usual care, annual screening or biannual screening. A critical review of this study indicates that several of today’s epidemiologic requirements, such as protocol adherence and avoiding a considerable variation in the applied diagnostic methods, would call such a conclusion into question. In addition, this conclusion was supported by the annually but not biannually tested study group. In an update of the study 6 years later, the authors (Mandel et al. 1999) described a 21% mortality reduction in the biannual screening group and presented slightly better results in an additional report 1 year later (Mandel et al. 2000). Hardcastle et al. (1996) claimed that the reduction in mortality
reported in several studies was observed not in unselected populations. They completed a randomized trial in which controls were not told about the study and received no intervention. Screening-group participants were sent a Hemoccult FOBT kit with instructions from their family doctor. In this randomized study a 15% reduction in mortality was confirmed. A similar reduction in mortality was reported for biennial screening by Kronborg et al. (1996). The result of this study was confirmed some years later in a 13-year follow-up evaluation (Jørgensen et al. 2002). It may be important to notice that only the screened patients but not controls received information about the study, like in the trial of Hardcastle et al. (1996). There is increasing evidence that the information itself can significantly influence the results of clinical trials (Porzsolt et al. 2004). This possibility makes it difficult to interpret the observed survival differences.

In the German survey, 85.1% of lesions with a size of 1–3 cm were completely removed. Advanced stages of adenomas including ‘Tis’ were found in 6.6% and cancer in 0.9% of the investigated persons. Most of the detected malignant lesions were at favourable cancer stages. Males with cancer were 2.5 years older, and women with cancer were 4 years older than other participants of the screening program (Zentralinstitut 2007).

Some years later, a re-analysis of published data reported that death due to colon cancer can be avoided in 1 of 862 screened persons (Moayyedi and Achkar 2006). This reduction in cancer-related mortality did not influence the overall mortality. A systematic review of the data on secondary colorectal prevention prepared by the Cochrane collaboration (Hewitson et al. 2007) confirmed a modest reduction in colorectal cancer mortality, a possible reduction in cancer incidence through the detection and removal of colorectal adenomas, and potentially, the less invasive surgery that earlier treatment of colorectal cancers may involve. Harmful effects of screening include the psycho-social consequences of receiving a false-positive result, the potentially significant complications of colonoscopy or a false-negative result, the possibility of over-diagnosis (leading to unpleasant and unnecessary investigations or treatment) and the complications associated with treatment.

A similar, rather reluctant interpretation of colorectal screening data was recently published (Kerr et al. 2007). This report confirmed the expected effect of FOBT screening but did not support the benefit of flexible sigmoidoscopy. These inconsistent reports demonstrate the difficulty of adequate interpretation of available scientific data. More advanced diagnostic techniques such as computed tomographic colonography are recommended by some groups (Kim et al. 2007) but may not yet be sufficiently standardized for use in large studies (Mulhall et al. 2005).

For the discussion of effectiveness it should be recalled that the concept of false-positive and false-negative results does not apply to colon cancer, as the therapeutic intervention (polypectomy) is integrated in two necessary tests (colonoscopy and histologic examination). Pseudodisease, however, may be a significant problem in colon cancer prevention but we are not aware of data that support reliable conclusions.

In the German study on colon cancer screening there were 2.7 complications per 1,000 investigations. Most complications (1.6/1,000) were due to bleeding, followed by cardiopulmonary complications (0.8/1,000) and perforations (0.3/1,000) (Zentralinstitut 2007). These complications have to be considered when assessing the value of colon cancer prevention.

An unsolved scientific problem concerns cases of spontaneous remission. According to our present understanding of the concept of malignant disease, such cases are difficult to investigate by a direct approach. Occasional cases of spontaneous remission are described in various types of cancer such as hepatocellular carcinoma (Ohtani et al. 2005), Hodgkin’s disease (Bang et al. 2005), lymphoma (Abe et al. 2007), melanoma
(High et al. 2005), and small cell lung cancer (Horino et al. 2006). As there are some indicators that neoplastic lesions of gastric cancer may not progress or even regress after eradication of *Helicobacter pylori* eradication therapy, spontaneous remission is discussed even in patients with precancerous gastric disease (Malfertheiner et al. 2006). If these spontaneous remissions would indeed occur more often in the early stages of a disease than in more advanced stages then they would have to be considered in the interpretation and understanding of secondary prevention. As this question cannot be answered without additional data, spontaneous remission may add additional uncertainty to the consideration of secondary prevention.

### 2.3.1.4 Value of Prevention Programs from the Public and Scientific Point of View

Women have a 1 in 12 risk (in the UK) or a 1 in 8 risk (in the United States) of developing breast cancer but only if they manage to escape other threats to life and survive to the age of 80. Incidence is not equivalent to mortality: In England and Wales, only one woman in 26 will have died of breast cancer by the age of 80 (Bunker et al. 1998). In the United States, breast cancer mortality has remained roughly constant since 1940 while incidence has nearly doubled (Harris et al. 1992). The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) data (Fig. 2.1) confirm these results.

These figures could indicate that therapy has effectively held back an epidemic of breast cancer. More likely these data indicate the problem of overdiagnosis and overtreatment. We are probably detecting some cases of breast cancer that existed before but which could not be detected by previous screening methods, nor did these cases of breast cancer affect their host. At present it is impossible to differentiate these inert cases of cancer (pseudodisease) from other cases of breast cancer that impair both their host’s length and quality of life. Since these two types of cancer cannot be differentiated, the detection and subsequent treatment of these
cases of pseudodisease may result in overtreatment in up to 20% of breast cancer cases detected by mammography.

This risk of overtreatment as well as the risk of false-negative and false-positive diagnoses has to be compared with the advantages of breast cancer screening. This assessment of value is rather complicated as it will be different from the public and the scientific point of view. Scientists may consider the only advantage of mammography the proportion of breast cancer deaths that can be prevented by it. We know from studies by Schwartz et al. (2004), however, that people in the general population value mammography high enough to accept the described false-positive and false-negative diagnoses. As more than 950 of 1,000 women who undergo mammography will finally get the expected “good news” that no cancer could be detected, we presume that this positive information is of considerable value for the tested population. This value of “perceived safety” (Porzsolt et al. 2007) may explain the demand of mammography despite its small benefit and considerable disadvantages.

Politicians are convinced that prevention and health promotion will improve health, quality of life and power. They promote prevention as societal task but not only as a task of health-care politics (Apitz and Winter 2004). Since such recommendations, which are not specific for a particular country, are supported by scientific statements it is almost impossible to find out whether or not the public’s perception of political information is justified by the original scientific data. Small changes in information introduced by the operator may considerably change its perception by the receiver. As all partners in the health-care system try to present their messages in the most positive frame, it can be expected that the information may not remain unchanged on its way from the place where it is generated, the scientific lab, to scientific publications and translation into a political statement, and then down to the final destination, i.e. the perception by the public.

### 2.3.2 Recommended Prevention Programs

#### 2.3.2.1 European Union

The 2003 explanatory memorandum (Health-EU 2003) of the “Europe Against Cancer Programme,” which was founded in 1985, includes three key elements. First, the partnership approach (bringing together all the national actors involved in all areas of cancer prevention); second, the code against cancer (10 rules for a healthy lifestyle, www.cancercode.org); and third, the long-term vision of lowering the cancer-specific mortality of the European population, originally set at 15% in the period of 1987–2000. The annual cancer-specific mortality in Europe actually fell by a total of 10%, equating to around 92,000 lives saved.

These key elements are based on the assumption that well-managed population screening is more effective than individual screening on demand. It follows that early detection of cancer by screening is one of the strategic areas of cancer prevention. It is also recognized that organized cancer screening should only be offered to healthy people if there is sufficient evidence that screening leads to a decrease in disease-specific mortality or the occurrence of advanced disease. Consequently, the following recommendations were released by the EU: mammography screening for breast cancer in women aged 50–69, faecal occult blood for colorectal cancer in men and women aged 50–74, and Pap smear screening for cervical abnormalities every 3–5 years, starting between the ages of 20 and 30. Other test may also be recommended once research shows that they meet the criteria for organized cancer screening.

#### 2.3.2.2 United States

The Agency for Healthcare Research and Quality (AHRQ) published recommendations for prevention programs in the United States. Their rec-
ommendations include screening for breast cancer, cervical cancer and colorectal cancer (U.S. Preventive Services Task Force 2007).

The United States Preventive Services Task Force (USPSTF) found fair to good evidence that several screening methods are effective in reducing mortality from colorectal cancer. The USPSTF concluded that the benefits from screening substantially outweigh potential harms, but the quality of evidence, magnitude of benefit, and potential harms vary with each method (U.S. Preventive Services Task Force 2002).

Screening for the genetic risk of breast and ovarian cancer is not recommended. The USPSTF found fair evidence regarding important adverse ethical, legal, and social consequences that could result from routine referral and testing of these women. The USPSTF concluded that the potential harms of routine referral for genetic counselling or BRCA testing in these women outweigh the benefits (U.S. Preventive Services Task Force 2005).

Screening for testicular cancer is not recommended as the low incidence of testicular cancer and favourable outcomes in the absence of screening make it unlikely that clinical testicular examinations would provide important health benefits (U.S. Preventive Services Task Force 2004a).

Screening for lung cancer is not recommended because its benefit has not been established in any group. The mortality rate of screening (due to the necessary biopsies) range from 1.3% up to 11.6% and morbidity rates can be as high as 44% (U.S. Preventive Services Task Force 2004b).

2.3.3 Critical Appraisal of Traditional Selection Criteria

Cancer incidence and mortality is presented in the introduction of most (secondary) cancer prevention programs. Although not stated explicitly these presentations may induce the impression that justification of secondary prevention depends on incidence and mortality. The increasing information and knowledge about variables that influence incidence data may lead to a more detailed interpretation of high incidence and not necessarily justify a secondary prevention program.

It is well known that the course of malignant diseases may vary considerably. The morphologic diagnosis is a poor predictor of the course of disease. Prostate cancer is a well-known example. Most prostate tumours grow slowly, do not produce metastases and do not affect the life of their hosts. Some cases of prostate cancer grow fast, metastasize in several organs, and impair the patient's quality and length of life. Similar biologic variation has been shown for other types of cancer such as breast cancer (Güth et al. 2006), B cell malignancies (Dave 2006) and cancer of the urinary bladder (Brauers and Jakse 2000). About 10 years ago it was commonly believed that patients with untreated breast cancer will die of breast cancer. Today we know that a considerable proportion of breast cancer cases are not life threatening to their hosts. This rather benign type of cancer is another example of pseudodisease. Although the proportion of pseudodisease is much smaller in breast cancer than in prostate cancer, management strategies including secondary prevention must be re-examined. In some circumstances, health services consume resources without producing added value. Inappropriate use of services might harm population health by taking limited resources away from programs that would have produced more benefit.

Besides pseudodisease, the scientific evidence that supports the possibility of spontaneous remissions should be discussed. This evidence is limited to single reports and partial reviews. Spontaneous remissions have attracted very little attention.

Several investigators have suggested that some tumours spontaneously regress. Because breast cancer is rarely left untreated, we know surprisingly little about the natural history of the
disease. In one analysis, Zahl and Maehlen (Zahl et al. 2004; Zahl and Maehlen 2006) attempted to piece together the natural history of breast cancer. They used a creative method for comparing age-matched groups of women living in four Norwegian counties. In 1996, these areas of Norway began screening women with mammography every other year. In the analysis, they considered the group that was screened three different times between 1996 and 2001. Eligibility was defined as being between the ages of 50 and 64 in 1996. For a comparison, they used women who were between the ages of 50 and 64 in 1992. In other words, rather than going to another locale to compare results, they went to another segment of time to get their comparison group. These women would have been screened three times between 1992 and 1997 if there had been a program. The women in the comparison group were all invited to receive a one-time “prevalence” mammogram. The “prevalence” mammogram is used to get a snapshot of how many women have breast cancer at any particular point in time. In this case a sample of women was invited for a test once the larger screening program began. In summary, the screened group had three mammograms while the comparison group had only one mammogram. Because of the slight time overlap of the two groups, the mammogram for the control group was given at the same age as the third mammogram for the screened group. We would expect, then, that the prevalence of breast cancer should be the same in the two groups. However, that is not what happened. The analysis suggested that the incidence of invasive breast cancer was 22% higher in the screened group than in the comparison group.

2.3.4 Incidence in Primary and Secondary Prevention

Although incidence is used to describe the rates of newly diagnosed cases in primary as well as secondary prevention, the interpretation of incidence is different in primary and secondary prevention (Fig. 2.2). In primary prevention, incidence describes the rate of diagnosed cases at the beginning of the prevention program. These incident cases represent the failures of a primary prevention program.

In secondary prevention, incidence usually describes the rate of cases detected by screening at the beginning of the program. As large cancer statistics, e.g. the report on cancer incidence and mortality in Europe (Boyle and Ferlay 2005), use incident data from different sources there is some risk that incident data from different sources may describe different populations. Some of these data may include patients who participated in secondary preven-

Fig. 2.2 Interpretation of ‘incidence’ in primary and secondary prevention. In primary prevention, incidence describes the rate of prevention failures at the end of the prevention program. In secondary prevention, incidence usually describes the rate of cases detected by screening at the beginning of the prevention (dots)
tion programs. These cases may include patients with pseudodisease and patients with spontaneous remissions. As incidence data based on screening are influenced by several additional variables such as the quality of the screening tools and the selected populations, it is rather difficult to interpret these data. In summary, incidence data have to be interpreted with caution and are not ideal predictors of successful prevention programs.

2.4 Discussion

There are several lessons we can learn from prevention studies. First, we need to understand the extent of our uncertainty about the benefits of prevention programs and share it with the public, patients and policymakers. No diagnosis/treatment process is free from risks. Application of treatment with no solid scientific evidence of benefit exposes patients to risk when there may be no potential gain. People invited to be screened for serious diseases must be told about the risks, benefits and limitations in a way that instils realistic expectations and ensures fully informed consent in those who participate (Gérvas Camacho 2002; Gérvas Camacho et al. 2007; Smith 1992). Public health policies in Europe focus on primary and secondary prevention and provide information on health factors. They claim that prevention and lifestyle can avoid some types of cancer and improve the health condition of the population (http://www.cancercode.org/). This view is derived from the somatic mutation theory of carcinogenesis, which includes several paradoxes (Baker and Kramer 2007) such as the presence of distinct precancerous lesions at the onset of promotion, the large number of genetic instabilities found in hyperplastic polyps that are not considered cancer, and spontaneous regression.

Second, “If we want more evidence-based practice, we need more practice-based evidence” (Green and Glasgow 2006). In other words, we need to conduct and carefully evaluate prevention studies to identify possible differences of expected efficacy derived from scientific reports and observed results in daily practice. It is not only the formal difference between a laboratory experiment and an ideal but artificial condition of a clinical trial and finally a real world situation which is perceived by scientists. Patient’s perceptions may influence the outcome. Patients are enthusiastic about screening and prevention. Such programs will motivate the patient to achieve the expected effects and not expected “side-effects” of prevention programs, e.g. perceived safety, hope, and a positive perspective. We assume that these side-effects of prevention programs will support the achievement of favourable outcomes. If, however, the time required to achieve a perceptible success of a prevention program is too long, the participant’s motivation and interest in the program may diminish. The effectiveness of prevention programs may be increased if we identify early success indicators and change the programs in a way that helps the patients to experience these early indicators of success, allowing us to reliably assess the achieved results.

Third, we should avoid repeating earlier mistakes by testing only hypotheses that are supported by mainstream assumptions. An example is the randomized German acupuncture study, which included more than 250,000 patients and 10,000 physicians. Several preliminary reports published between 2004 and 2006 indicated that acupuncture is being successfully applied in a variety of patient groups even though the underlying mechanism is not understood (Szczurko et al. 2007; Tournaire and Theau-Yonneau 2007).

The lessons discussed in this paper suggest that different types of predictors may be used to identify successful prevention programs (Table 2.1).

First and most importantly, epidemiologic indicators are needed to confirm at least some causal relationship of the planned prevention program and the expected outcome. These indi-
The predictors listed in Table 2.1 summarize three issues which are discussed in this paper and might be considered when planning new cancer prevention programs. Epidemiologic criteria have to demonstrate efficiency and the high quality of the planned intervention. Social criteria can be used to assess the support of the program by the social environment; and finally, individual criteria will help to estimate the chances that a prevention program will succeed.

Table 2.1 Predictors of successful prevention programs. The success of prevention programs depends primarily on epidemiologic predictors which are different for primary and secondary prevention. Successful prevention programs have to meet social and individual predictors as well. These predictors are the same in primary and secondary prevention.

<table>
<thead>
<tr>
<th>Types of predictors</th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
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<tbody>
<tr>
<td>Epidemiologic predictors</td>
<td>Causal relationship of expected outcome and of:</td>
<td>Screening and therapy</td>
</tr>
<tr>
<td>Social predictors</td>
<td>Public acceptance, political decisions, advice of health care professionals, recommendations of family and friends</td>
<td></td>
</tr>
<tr>
<td>Individual predictors</td>
<td>Personal preferences and values, acceptance of scientific and social recommendations</td>
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</tbody>
</table>

The predictors are different in primary and secondary prevention. In primary prevention these indicators are related to changes of lifestyle or behaviour (or both). In secondary prevention these indicators have to confirm the quality of disease management (Mayer and Mayer 2004; Stagmo et al. 2004; Campbell 2004) while confirming the effectiveness of the screening methods, as assessed by sensitivity and specificity as well as of the treatments. Treatments are adequately assessed by testing effects on survival and on quality of life. The efficiency of treatment in early stages of cancer cannot always be predicted from experience with advanced stages. Extending survival in prostate cancer (Antonarakis et al. 2007) will generate added value if it can be related to new treatment modalities rather than to new selection strategies. However, distinguishing these differences will be difficult. Lung cancer is not a good candidate for secondary prevention because screening does not lead to treatments that enhance health outcomes.

Depending on the point of view, confirmation of the quality may also include the efficiency of diagnostic tests and treatment methods. Efficiency may be related to monetary, i.e. tangible, costs as well as to intangible costs such as side-effects or invasiveness of the procedure.
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