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The history of cancer screening

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"Those who do not appreciate history are destined to repeat it"

George Santayana

The early detection of cancer holds intuitive appeal. There is a deeply-rooted belief in American society that screening to detect cancer early is invariably beneficial, and evidence to the contrary is often viewed with skepticism. However, cancer screening is a complicated science, and many of its principles are counter intuitive. Screening is also a public health intervention. Appropriate screening technologies, when used properly, have the potential to prevent thousands of cancer deaths. On the other hand, there is such a thing as nonbeneficial screening, and this can cause tremendous harm.

Every medical intervention has the potential for both benefit and harm. Cancer screening is no different. Beneficial screening has the potential to lower cancer-specific mortality, and if precursor lesions are detected and removed, it can reduce cancer incidence. Even then, there is risk and the potential for harm. These include overdiagnosis (discussed later in this monograph), false-positives, the inconvenience of the screening test, unnecessary diagnostic tests after a false-positive screen, and the potential harms of diagnostic testing, and treatment. Even beneficial screening technologies can occasionally result in some deaths.

The decision to use a screening test or to institute a screening program should involve a balancing of the proven benefits and harms. The benefit/risk ratio of a screening test and screening program are of utmost public health significance, as screening targets huge asymptomatic populations and the risks associated with screening can adversely affect large numbers of individuals.

In the history of American medicine, many screening tests have been widely adopted based on theoretical benefit and before adeqate investigation to demonstrate benefit and assess harm. The rush to screen has led to countless numbers of patients receiving unnecessary treatment

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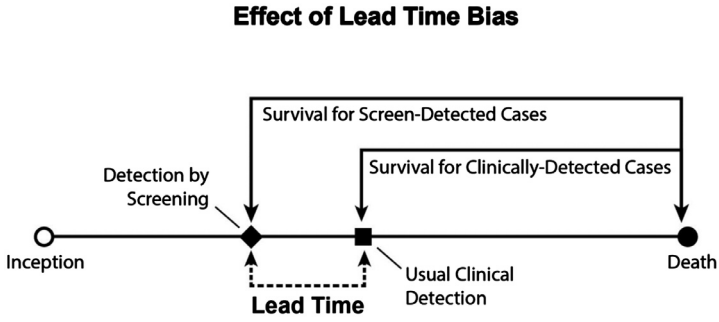

Fig. 1. Effect of lead time bias.

and the harms associated with it. We are entering a period of unprecedented development of cancer screening tests using molecular biology and other technologies. Hopefully, a review of the history of screening will prevent the mistakes of the past from being repeated.

Advocacy for early diagnosis began in the mid 19th Century. The British physician Horace Dobell proposed a thorough routine history and physical examination "to discover the earliest defect in the physiological state".[1] This was a call for early detection of disease in general, and not specific to cancer.[2] In 1907, the American Dr. Charles Childe advocated early detection of cancer in his book entitled *The Control of a Scourge, Or How Cancer Is Curable*.[3] Childe declared the majority of cancers curable with early detection. At the time, there were no imaging studies and few laboratory tests. Careful physical examination was advocated as the primary early detection tool.

In the 1920s, The American Medical Association (AMA) endorsed use of the periodic health examination for early detection of a number of diseases including cancer.[4] It was about this time that the word "screening" entered the medical vernacular. At the time there really were no formal clinical trials, and medicine was influenced by professional opinion, some of which was influenced by anecdotal case reports and case series.

In the first half of the 20th century, screening tests were adopted based only upon expert opinion that the test was good. There was no scientific assessment of early detection efforts beyond "the tumor was found; the tumor appeared to be localized; the tumor was treated." The few published reports with outcomes noted longer survival with screen-detected cancer, sometimes noting longer survival even when the patient died of the screen-detected cancer.

The belief in early detection began spreading into the lay community about the time of the founding of the American Society for the Contol of Cancer (ASCC) in 1913. The ASCC would change its name to the American Cancer Society in 1945. The Women's Field Army of the ASCC was formed in the 1930s.[5] This army of 150,000 women went neighborhood by neighborhood teaching the virtues of early detection of cancer (Fig. 1). The Field Army focused on educating the public on the early warning signs of cancer and breast self-examination. The idea was to encourage people to realize a warning sign and seek medical help. One famous slogan of the Women's Field Army was "Delay Kills!!" The ASCC and its early community public health interventions would be pivotal in creating a positive public perception of cancer screening and early detection that lasts to this day.

Although the initial screening test was the physical examination, technical innovation over time has led to the introduction of a number of diagnostic tests. Diagnostic tests are administered to patients with a suspicion of disease to aid in confirming a diagnosis.[6] Some diagnostic tests have become screening tests. A screening test is performed in an asymptomatic person to determine if there is reason to do further diagnostic testing to find cancer. Tests that were originally diagnostic and have become screening tests include the Pap smear for cervical cancer, the chest radiograph for lung cancer, the spiral computed tomography (CT) scan for lung cancer, the mammogram for breast cancer, and various endoscopic procedures for colon cancer.

Assessing the evidence

Over the past 50 years there has been a growing movement away from reliance on observation and intuitive thinking to justify use of a screening test. This has been accompanied by the emergence of evidence-based medicine and formal methods of assessment of the efficacy of screening and methods to measure the effect of screening on the population. The statistical principles and clinical trials methodology to demonstrate the efficacy of a screening test were developed in the 1950s and 1960s. The prospective randomized trial is now accepted as the gold standard for demonstrating the efficacy of a screening intervention. The first prospective randomized trial was reported by Sir Austin Bradford Hill in 1948 to assess the efficacy of streptomycin for tuberculosis.[7]

Even after these principles of evidence-based screening were well defined, there was widespread dissemination and adaptation of screening technologies such as prostate specific antigen (PSA) screening for prostate cancer and low dose spiral CT for lung cancer before rigorous assessment of the tests' utility for screening. Some have argued that it is ethically unacceptable to do nothing in face of continuing deaths while clinical trials are under way, yet it is important to realize that some screening tests have been found net harmful once appropriately evaluated.

Theoretical considerations

Cole and Morrison proposed that 3 conditions must be met before cancer screening is considered as a public health measure.[8] First, for the specific cancer of interest, treatment should be more effective in screen-detected than clinically-detected cases. If there is no effective treatment or treatment is equally effective in screen-detected and clinically-detected cases, then screening will offer no advantage. Secondly, the cancer of interest should have a high prevalence and, finally, it should have a sufficiently high mortality or morbidity to justify the costs of implementation of a large scale screening program[9].

The total preclinical phase (TPCP) is the period of time from initiation of cancer to the onset of symptoms.[8,10] The TPCP is generally not known, but the detectable preclinical phase (DPCP) is a component of the TPCP and is the period of time from when the cancer is detectable with a screening test until the time it was destined to become clinically detectable.[8,10] The sensitivity of a screening test is its ability to correctly identify individuals who have the specific cancer of interest (true positives/total with disease). Conversely, specificity refers to the ability of a screening test to correctly identify individuals who do not have the cancer of interest (true negatives/total free of disease). Sensitivity and specificity in theory are independent, but in practice they are often inversely related.[6] That is, as the sensitivity increases, the specificity decreases, and vice versa.

The efficacy of cancer screening can only be determined by a randomized screening trial, in which 1 group is selected at random to be screened, and the other serves as unscreened controls. Such trials have been undertaken in various countries around the world for breast, colorectal, prostate, lung, ovary, cervix, oral, and liver cancers, and the findings are discussed below and summarized in Table 1. In addition, over the years, numerous case-control and observational studies have addressed the effectiveness of cancer screening in various populations. However, case-control studies can only assess the effect of screening in those screened and cannot avoid selection bias. There are several biases associated with observational studies and 3, in particular, should be carefully considered: lead-time, length, and selection bias[11]. Moreover, both the randomized trials and observational studies indicate potential harms associated with screening.[12,13]

Lead-time

Survival refers to the time interval from cancer diagnosis to death. As screening advances the time of diagnosis, it will invariably appear to improve survival, even if it does nothing to

Table 1
Randomized trials on cancer screening.

Specific cancer	Randomized trial	Trial design
Breast	HIP	MM+CBE vs UC
	Malmo	MM vs UC
	Two-County	MM vs UC
	Stockholm	MM vs UC
	Gothenburg	MM vs UC
	Edinburgh	MM+CBE vs UC
	Canada NBSS I	MM+CBE vs UC
	Canada NBSS II	MM+CBE vs CBE
	United Kingdom Age	MM vs UC
	Shanghai	BSE vs UC
	St. Petersburgh	BSE vs UC
	Mumbai	CBE vs UC
	Kerala	CBE vs UC
	J-START (Japan)	MM+US vs MM
Colorectal	Minnesota	FOBT vs UC
	Nottingham	FOBT vs UC
	Funen	FOBT vs UC
	Gothenburg	FOBT vs UC
	Norway	Flex Sig vs UC
	United Kingdom	Flex Sig vs UC
	Italy	Flex Sig vs UC
	USA PLCO	Flex Sig vs UC
Prostate	PLCO	PSA vs UC
	ERSPC	PSA vs UC
Lung	Memorial Sloan-Kettering	SC vs UC
	Johns Hopkins	SC vs UC
	Mayo Clinic	SC+CXR vs UC
	Czech	SC+CXR vs UC
	PLCO	CXR vs UC
	NLST	Low dose CT vs CXR
	NELSON	Low dose CT vs UC
Ovary	PLCO	TVU+CA-125 vs UC
	UK	TVU+CA-125 vs UC
Cervix	Osmanabad	HPV vs cytology vs VIA vs UC
	Mumbai	VIA vs UC
	Dindigul	VIA vs UC
Oral	Kerala	Visual inspection vs UC
Liver	Qidong	AFP vs UC

Randomized trials published in the peer reviewed literature.
Abbreviations: AFP, alpha-fetoprotein; BSE, breast self-examination; CBE, clinical breast examination; CT, computerized tomography; CXR, chest X-ray; ERSPC, European Randomized Study of Screening for Prostate Cancer; FOBT, fecal occult blood testing; Flex Sig, flexible sigmoidoscopy; HIP, health insurance plan; HPV, human papilloma virus; J-START, Japan Strategic Anti-cancer Randomized Trial; MM, mammography; NLST, National Lung Screening Trial; PLCO, prostate, lung, colon, ovary; PSA, prostate-specific antigen; SC, sputum cytology; TVU, transvaginal ultrasound; UC, usual care; vs, versus; VIA, Visual inspection with acetic acid

delay the time of death (Fig. 1). Lead time refers to the time between screen detection and usual clinical detection (i.e., it corresponds, on average, to one half the DPCP), and may lead to the erroneous conclusion that screening prolongs life, when in fact it simply extends the period of time over which the cancer is observed.[14] Thus, studies showing that screening improves survival are flawed if they fail to account for lead time.

Although most patients diagnosed with cancer will gain lead time as a result of screening, only a few will benefit from it. Many individuals die from other causes unrelated to their cancer diagnosis, regardless of whether the cancer is detected with screening or following symptoms. In other instances, screening may do nothing to delay the time of death from cancer, but only provide advanced knowledge of impending death. The extra lead time gained from screen-

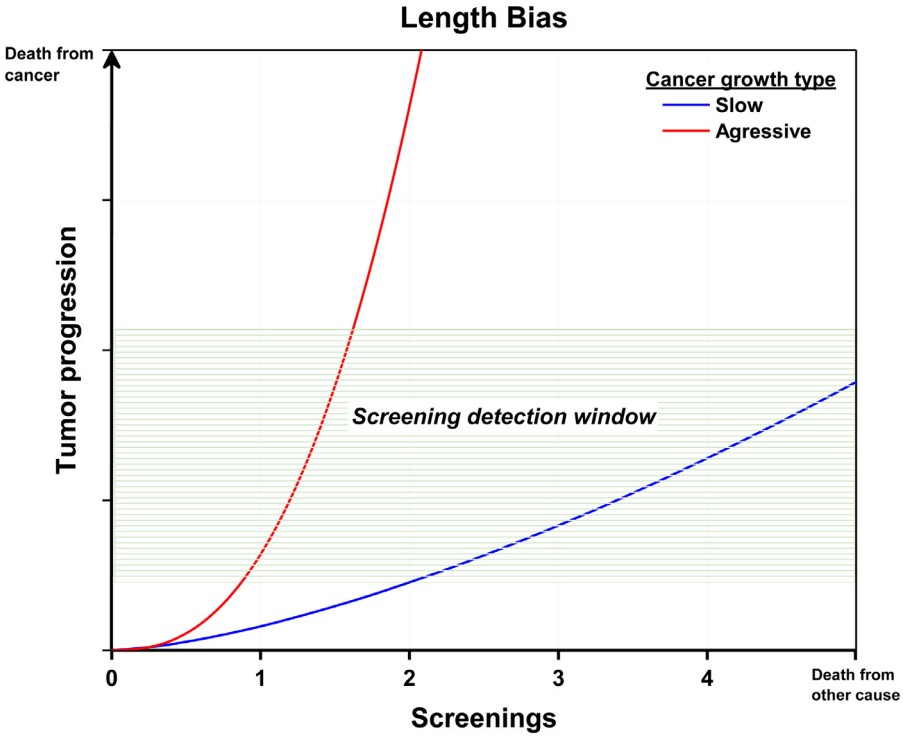

Fig. 2. Effect of length bias.

ing may adversely affect the quality of life (i.e., increase the period of anxiety and financial hardship).

Length bias/over diagnosis

Length bias refers to the fact that slower-growing cancers (i.e., those with more favorable biological features) exist for a longer period of time in the DPCP and are therefore more likely to be detected with screening (Fig. 2).[8,15] In contrast, faster-growing cancers (i.e., those with less favorable biological features) are more likely detected clinically in the intervals between screening sessions. Thus, there are often biological differences between screen-detected cancers and those detected clinically.[16] Screen-detected tumors are generally more indolent, whereas interval tumors (detected clinically) are more aggressive.

In observational studies, the better outcomes of patients with screen-detected cancers might at least partly be attributable to length bias. In the extreme, length bias can result in "over-diagnosis," which refers to the detection of cancers that would never have been diagnosed in that person's lifetime in the absence of screening.[17] A competing cause of death may shorten the full natural history of cancer, particularly in the elderly, who might have died of other causes before a screen-detected cancer became evident. Moreover, it has even been suggested that some screen-detected cancers might have undergone spontaneous regression.[18] In the Canadian National Breast Screening study, most of the impalpable breast cancers detected by mammography alone were estimated to have been overdiagnosed.[19] Also, in the United States, it has been argued that nearly one third of all breast cancers might never have been diagnosed in the absence

of mammography screening.[13,20] Thus, cancer screening is potentially associated with a substantial risk of over-diagnosis, and this may result in unnecessary anxiety, financial hardships, and excess morbidity and mortality from unnecessary treatments (see below).[21]

Selection bias

In general, cancer screening programs attract health-conscious individuals with good access to healthcare.[22] Such individuals generally have a longer life expectancy and better health outcomes, regardless of screening, referred to as the "healthy-screening" or "healthy volunteer effect."[23] Selection bias should be considered in any nonrandomized comparison of outcomes between individuals who undergo screening vs those who do not.

To eliminate the effects of lead time, length, and selection biases, the efficacy of cancer screening should ideally be determined in randomized controlled trials with all-cause mortality as the endpoint.[24] All-cause mortality is an unambiguous endpoint and eliminates the risk of bias in the assessment of cause of death. Yet, it is not a practical endpoint for a cancer screening trial because it generates a huge sample size requirement over long periods of time (i.e., hundreds of thousands of individuals would be required for each trial). To reduce the sample size requirement, cancer-specific mortality is generally utilized as the endpoint, but even so, tens of thousands of individuals are generally required for each trial. Additionally, 2 forms of assessor bias should be considered whenever cancer-specific mortality is utilized as an endpoint: sticky-diagnosis bias and slippery-linkage bias.

Sticky-diagnosis bias

The target cancer is more likely diagnosed in the screened group than the control group, and deaths from the target cancer are therefore more likely to be ascribed to the screened group. Thus, deaths from other causes in the screened group might falsely be attributed to the target cancer. This is referred to as sticky-diagnosis bias and it may result in an excess of cancer-specific deaths reported in the screened group, leading to an underestimation of the benefit of screening.[25]

Slippery-linkage bias

Cancer screening involves medical interventions that may potentially result in occasional deaths, but these deaths are generally not attributed to the target cancer. Thus, screening may lower cancer-specific deaths but increase deaths from other causes (i.e., deaths from medical interventions associated with screening). This is referred to as slippery-linkage bias, and it may result in an overestimation of the benefit of screening in randomized trials with cause-specific mortality as the endpoint.[24]

The issue of slippery-linkage bias underscores the potential for morbidity and mortality with screening interventions. For example, colonoscopy is widely used in the United States to screen for colorectal cancer, but it has also been associated with low rates of serious (and potentially life-threatening) complications.[26,27] Screening mammography is widely used to screen women at high risk for breast cancer. Yet, in women below the age of 30 who are BRCA 1 and BRCA 2 mutation carriers, the low-dose radiation associated with screening mammography may increase the risk of developing breast cancer[28]. Also, cancer screening generally only identifies potentially suspicious lesions, and additional interventions, including surgery, are required to establish the diagnosis. These additional interventions carry risk, including the risk of infection, bleeding, anesthetic complications, and even occasional deaths.

Both sticking-diagnosis and slippery-linkage biases can be overcome in a trial which incorporates carefully designed reviews of cause of death.[29]

False-positives

False-positives are those cases reported as suspicious or malignant with screening that, on further evaluation, prove to be benign. In the United States, approximately 10.7% of all screening mammograms lead to a false-positive result[30]. In the Prostate, Lung, Colon, Ovary (PLCO) trial, participants were subjected to multiple cancer screening tests, and after 14 screening tests, the risk of at least 1 false-positive result was 60.4% (95% confidence interval [CI]: 59.8%-61%) for men, and 48.8% (95% CI: 48.1%-49.4%) for women[31] . False-positives result in additional medical interventions to establish a diagnosis, and therefore not only increase healthcare costs, but also the potential for morbidity and mortality from these interventions. Moreover, false-positives lead to unnecessary patient anxiety, and data from the National Health Interview Survey suggests that this anxiety persists for many years after the false-positive result and may dramatically lower the quality of life.[30]

The history of screening for specific cancers

Cervical cancer

Irish physician Walter Hayle Walshe developed the field of cytology in the mid 19th century. The Romanian Aurel Babes used a platinum loop to collect cervical cells and detect the presence of cancer. In the late 1920s, Georges Papanicolaou introduced a slightly different, easier-to-perform procedure.[32] This method, now known as the Pap smear or Pap test, is also fairly easy to interpret.

In the 1930s, Dr. Papanicolaou advocated use of the pap test as a diagnostic test. At the same time, cervical pathology was not standardized. Work to define cervical dysplasia as distinct from cervical cancer was incomplete.[33] There was controversy about the treatment of dysplasia and limited-stage cervical cancer. Many gynecologists treated preinvasive epithelial carcinomas (carcinoma in situ) as well as dysplastic lesions that would now be called cervical intraepithelial neoplasia (CIN) 1 or CIN 2 with radical hysterectomy or radiation therapy. Radical hysterectomy is removal of the uterus, cervix, the surrounding tissues, and lymph nodes.

In 1943, Papinicolaou published his Atlas of Exfoliative Cytology,[34] a treatise containing comprehensive information on the cytology of both healthy and diseased tissue. The *Atlas* explains that the Pap test can screen for cervical abnormalities that could be cancer or could progress to cancer. This was the first call to use the test for screening. Cervical cancer screening programs were rapidly implemented in the late 1940s.

In 1948, the American Cancer Society sponsored “The First National Cytology Conference” in Boston.[32] At this meeting, Dr. Papanicolaou trained pathologists to read Pap smears. Diffusion of cytologic technology was also supported by the National Cancer Institute and the US Public Health Service. The US Public Health Service commissioned a large-scale cervical cancer screening demonstration project involving more than 108,000 women in the southern United States.[35] This observational study showed that mass screening with the Pap test was feasible, and diagnosed a substantial number of women with cervical pathology. Yet the demonstration project was not designed to show that screening reduces mortality.

The American Cancer Society became a driving force promoting the Pap test. The society produced public service advertisements in print and on television to change attitudes and promote cervical cancer screening. In 1965, the Society would win a special Emmy award for placing a cervical cancer screening story in the script of a popular television soap opera. Throughout the 1960s, organized Pap smear screening programs were launched in the United States, Canada, and Scandinavian countries except Norway.[36]

Significant reductions in cervical cancer incidence and mortality were observed by the late 1970s in those countries that had implemented this screening strategy in the late 1950s.[36,37] Interestingly, an organized Pap smear screening program was launched in the UK in the 1980s, and reductions in cervical cancer mortality became evident just a few years later.[38] These were ecologic observations. Ecologic observations are useful but potentially biased.[39]

Newer cervical screening technologies

The first prospective randomized studies of cervical cancer screening was initiated in 1998. In the Osmanabad district in India, a cluster-randomized trial was initiated to assess the efficacy of 3 different cervical cancer screening strategies.[40] More than 131,700 women were randomly assigned to 1 of 4 screening groups: testing for active human papillomavirus (HPV) infection, cytological testing, visual inspection with acetic acid (VIA), or usual care. A significant 48% reduction in cervical cancer mortality rate was observed in the group tested for HPV infection compared to the usual care group (hazard ratio 0.52; 95% CI: 0.32-0.69).

In 1998, a cluster-randomized trial was initiated in Mumbai, India to assess the efficacy of VIA screening. In this study, 75,360 women randomized to VIA screening vs usual care.[41] The screened group experienced a 31% reduction in cervical cancer mortality (rate ratio [RR] = 0.69; 95% CI: 0.54-0.88; $P = 0.003$), demonstrating that VIA screening by primary care workers is a potential means of lowering cervical cancer mortality in low-resource settings. VIA screening was also found effective in another cluster randomized trial in Dindigul District, India.[42]

In the mid 1990s, newer technologies such as liquid-based cytology (e.g., ThinPrep) were introduced and are now widely used. Conventional Pap smears are read by a cytotechnician. Liquid-based cytology is machine read and may be more objective, as the machine does not fatigue through a day of reading smears. A definite advantage of liquid-based cytology is that HPV testing can be done on the sample. However, liquid-based cytology is more expensive than conventional Pap testing, and to date no study has examined whether liquid-based cytology is more effective than conventional Pap testing.

The US Food and Drug Administration (FDA) has approved several screening tests that detect DNA or RNA of oncogenic HPV (evidence of active infection). HPV testing is approved: (1) as a second test following an equivocal cytology result and (2) for primary screening in conjunction with cervical cytology in women aged 30 years and older.[43] At this time, HPV DNA screening alone is not approved in the United States. In the future, it may become standard for women older than 30 years of age. Compared to cytology alone, the combination of HPV and cytology has 95%-100% sensitivity for detecting moderate dysplasia, but it has a relatively low specificity. The higher number of false-positive findings leads to an increased rate of colposcopy.[44,45]

The Pap smear was developed in the 1920s and 1930s as a diagnostic test. Cervical cancer screening using the Pap smear was adopted in the 1940s based on the principle that early detection and treatment must be good. Nearly 25 years after the widespread introduction of cervical cancer screening, it became clear that cervical cancer incidence and mortality were declining.

The broad introduction of the Pap smear came about at a time when there was significant discordance in the reading of cervical cytology and a lack of understanding of the biologic behavior of dysplasia. Some women with cervical dysplasia were treated with hysterectomy or radiation therapy as if dysplasia were invasive cancer. In the late 1950s and early 1960s evidence was developed to suggest that ablation of the dysplastic cervical lesion is often as good as radical hysterectomy. Dysplastic (precancerous) lesions were treated with ablation by electrocautery, and later by cryotherapy or laser ablation. These procedures can weaken cervical competence and lead to fertility and pregnancy complications. Today a great deal more is understood about cervical pathology, and especially the behavior of dysplasia. From its inception until the 1990s, there were significant differences among physicians in cervical cytology reporting. The Bethesda System was implemented in the 1990s to bring some standardization.[46] We now recognize that what are now referred to as CIN 1 lesions are nonobligate precursors of cervical cancer. Most will spontaneously regress within 1 year. Indeed, most CIN 2 lesions behave in similar fashion.[47]

Breast cancer

The first reported use of X-rays to image breast cancer was in 1913. In the period between 1930 and 1955, some academic centers used a form of mammography as an adjunct to physical examination after detection of a suspicious mass for the diagnosis of breast cancer.[48] Innovations from Houston radiologist Robert L. Egan dramatically improved mammography. In the late 1950s, he used a low-voltage technique, a fine-grain intensifying screen, and industrial film to generate mammographic images that were clearer and easier to interpret.[49] Egan then went on to show the value of mammography in a study of 1000 women presenting to a breast clinic. Of the 245 breast cancers confirmed by biopsy, 238 were identified by mammogram. There were 19 women with breast cancers not found on physical examination.[50] There were several more case reports of women being diagnosed with small tumors that were not palpable on examination. Anecdotal evidence that screening found tumors early was becoming persuasive since it was assumed that all untreated tumors kill .

The late 1950s was also a time of advancement in statistical methodologies. The radiologist Phillip Strax with the Health Insurance Plan of Greater New York proposed that breast cancer screening using the Egan technique be submitted to formal evaluation. Strax along with epidemiologist Sam Shapiro and surgeon Louis Venet designed and launched the Health Insurance Plan of New York (HIP) breast screening study,[51] a prospective randomized trial. More than 62,000 women aged 40-64 years were randomized to clinical breast examination and mammogram or usual care, which for some women included clinical breast examination. By 1971, the breast cancer death rate of the screened cohort was 40% lower than that of the control group. This study confirmed that screening with subsequent treatment was associated with a mortality reduction. Later evaluation would place this reduction at 30%.[52]

The investigators also noted that 70% of the cancers in the screened arm were node-negative vs45% in the control group. At the time, this stage shift was thought evidence of screening benefit. A stage shift is consistent with benefit, but is not proof of benefit. Applying today's understanding of cancer biology, an increase in the incidence of localized cancer without a drop in the incidence of regional and distant disease is evidence of overdiagnosis.[53,54]

Interpretation of the HIP results was controversial, especially for women in their 40s. Analysis by age stratification show that mortality reduction occurred in women age 50 years and above. Some experts advocated further study of screening in women aged 40-49. Some even felt the HIP was not definitive even for women aged 50-64 at entry.[55] Screening mammography advocates rejected this. Buoyed by a continued decline in cervical cancer mortality attributed to the decision to encourage Pap testing in the 1950s and 1960s, they began urging mammography screening for women as young as age 35 even though HIP enrolled only women age 40 years and older.

In 1972, the American Cancer Society and National Cancer Institute launched the Breast Cancer Detection Demonstration Project (BCDDP).[55] This demonstration project would enroll 270,000 women aged 35-74 years in 29 sites. Enrollment accelerated in 1974 after First Lady Betty Ford, and the wife of the Vice President, Margaretta (Happy) Rockefeller, announced they had been diagnosed with breast cancer through mammography.

The BCDDP was controversial. By 1977, 506 so-called "minimal" breast lesions of less than 1 cm in diameter had been found in BCDDP participants. In 1 audit by a reference pathologist 66 of the 506 lesions were not invasive cancer nor carcinoma in situ. Most of the 66 women had already received the definitive therapy of the time, which was radical mastectomy.[56]

In an audit of mammography equipment in the BCDDP done in the late 1970s, radiation dose was found to be highly varied and far too high in some sites.[57] Quality of mammography was a serious issue as mammography became more popular in the United States. The FDA Nationwide Evaluation of X-ray Trends (NEXT), a 1985 survey of mammography facilities, found that 36% of facilities were producing mammographic images of unacceptable quality.[58] In fact, 15% of facilities were using general purpose X-ray equipment for mammography.[59] In 1987, the American College of Radiology introduced voluntary accreditation for mammography facilities; one third of facilities failed on their first application for accreditation. The Mammography Quality Standards

Act was enacted in 1992. It required the FDA establish and enforce quality standards for all US mammography facilities. In an FDA survey of more than 10,000 facilities operating in December, 1994, one fourth had significant violations.[60,61]

Since the mid 1990s each mammography facility must be certified and inspected once per year by FDA-supervised inspectors. The inspection assesses documentation of the credentials and training of the physicians, technologists, and physicists working in the center, the calibration of the equipment, maintenance of medical records, and mammography outcomes. In 2016, 11.7% of more than 8700 mammography facilities were found to have a significant violation.[62]

Analysis of the randomized breast cancer screening trials

Ultimately, 9 randomized trials were undertaken to assess the efficacy of mammography screening for breast cancer: The Health Insurance Plan (HIP), the Swedish Two-County study, Malmo, Gothenburg, Stockholm, Edinburgh, the Canadian National Breast Screening Study (CNBSS) I, CNBSS II, and the United Kingdom Age Trial.[52,63-70] In total, approximately 661,000 women were recruited into these 9 trials, with ages at entry ranging from 39 to 74 years (Table 1).

These trials had very different designs. Participants in the Swedish breast clinical trials were randomized such that those in the control arm did not know they were in a trial.[71] This means that those in the intervention arm had more contact with healthcare providers and were more able to get care should they find an abnormality between annual screens. Those in the control arm would have been less educated about the disease being studied and less likely to recognize symptoms. They may have been more difficult to follow and more likely to be lost to follow-up. All of these are biases would favor a finding that screening is more effective.

The accessibility of clinical trials data for audit and verification also vary. Formal external audit has been undertaken in the Canadian trials[72,73]; audits of the very positive European trials have not been published, if conducted. The earlier mammography screening trials suggest that the optimal benefit of mammography screening is for women aged 50 to 69 years at entry, with a 25% to 30% reduction in breast cancer mortality occurring within 7-9 years after initiation of screening.[64] A major contributor to these data was the Swedish Two-county trial. This trial was cluster randomized, and long-term follow-up shows continued widening of the difference in cumulative breast cancer mortality between women who were screened vs not screened, suggesting that there was an initial imbalance between the 2 groups.[64]

There is an age interaction with respect to the efficacy of mammography screening. For women younger than 50 of age at entry, the apparent benefit of mammography screening is less, takes longer to emerge, and may potentially be attributable to continued screening past age 50 years.[74] Two more recent trials were designed to specifically address the efficacy of mammography screening in women aged 40-49 years (CNBSS I and the UK Age Trial). They found no benefit.[69,70] One would expect mammography would be a better test for older women based on principles of screening. The accuracy of a screening test, its positive predictive value, improves as the prevalence of disease increases. The prevalence of breast cancer increases with age. Sensitivity and specificity of mammography are also lower in younger women because density is more common in younger women. Density makes it more difficult to see the lesion.

There also remains uncertainty as to when mammography screening should stop.[75] Only the Swedish Two County and Malmo trials included women aged 70 and older, and a subgroup analysis found no benefit for screening women aged 70 years and over.[76,77]

A historical overview of the 9 mammography screening trials also reveals a perplexing trend. The greatest benefit of screening is evident in the older trials. The oldest trial, HIP, initiated in 1963, demonstrated a 30% reduction in breast cancer mortality with screening mammography, while the 3 most recent trials (CNBSS I, CNBSS II, and the UK Age trial) show no benefit.[52,69,70] This might partly be explained by the increase in breast cancer awareness over time and the resultant reduction in the average size of tumors detected in the control arms of these trials. Also, third-generation adjuvant systemic therapy was freely available to women enrolled in the

3 most recent trials, but not the earlier trials, and improvements in therapy are probably reducing the absolute benefit of breast cancer screening.[78,79]

To demonstrate how the benefit of screening diminishes as treatments improve, let us assume that screening has a 25% relative benefit and therefore reduces the risk of breast cancer death from 40% to 30% over a 20-year period (i.e., a 10% absolute benefit). Now let us assume that an adjuvant therapy regimen with a 20% relative benefit becomes available. For those patients with an initial 40% risk of death, this adjuvant therapy regimen would reduce the risk of death to 32%, and the absolute benefit of screening would therefore be reduced from 10% to 8% (i.e., 25% of 32%).

Greater progress has been made in the treatment of estrogen-receptor (ER)-positive vs ER-negative breast cancers. Screening preferentially detects slower growing cancers that spend a greater length of time in the preclinical phase, meaning that it preferentially detects ER-positive tumors. This is known as length bias.[80] The relative proportion of ER-positive to ER-negative breast cancers has been increasing for at least 2 decades, partly due to mammography screening. However, the incidence of ER-negative breast cancers has also been decreasing at a rate of 2% per year for at least 2 decades in the United States, so the relative increase in ER-positive cancers could also reflect an absolute decrease in ER-negative tumors.[81]

In addition to improvements in breast cancer treatment over the past 50 years, the female population being screened may also be changing. It is certain that the prevalence of breast cancer risk factors are changing. Some of these risk factors may be risk factors specifically for ER-positive or ER-negative disease. Changes in diet and exercise habits have led to the population having a lower median age at menarche and increased the prevalence of obesity. In addition, patterns of pregnancy and hormone usage have changed.

The population effects of breast cancer screening

Today, approximately 60% of American women older than 40 years have had a mammogram in the past 2 years. In the United States, approximately 10.7% of all screening mammograms lead to a false-positive result.[30] The proportion of false-positives is higher for first mammograms or when previous mammograms are not available for comparison.

Overdiagnosis, as mentioned previously, refers to the detection of cancers that pose no threat to life, and that would never have been detected in the absence of screening.[21] A number of studies have demonstrated overdiagnosis in breast cancer, with the proportion representing overdiagnosis being estimated as between 10% and 50%. Most studies suggest that the prevalence of overdiagnosis is 15% to 25%.[20,53,82] The proportion overdiagnosed is likely smaller in younger women and higher in older women.

Mammography, of course, involves radiation exposure. In a simulation study performed for the US Preventive Services Task Force, it was estimated that annual 2D digital screening of 100,000 women, age from 40 until age 74 years, would induce 125 breast cancer cases (95% CI: 88-178) and lead to 16 deaths (95% CI: 11-23).[83] The same simulation projected 968 breast cancer deaths averted by early detection from screening. Women with large breasts requiring extra views for complete examination (8% of population) were projected to have a greater radiation-induced breast cancer risk (266 cancer cases and 35 deaths per 100,000 women). Biennial screening starting at age 50 years reduces the risk for radiation-induced cancer 5-fold.

Observational data in Europe and Canada have suggested that the mammography benefit seen in the meta-analyses of the mammography screening trials is replicated in population-based statistics.[84] These studies suggest that mammography leads to a 20% to 40% reduction in mortality. It should be remembered that observational studies are prone to bias and other confounding factors. If screening is a major contributor to the reduction in breast cancer mortality in these countries, then there should also be a reduction in the rates of advanced breast cancer at diagnosis, but this is not evident.[13,85]

The United States has experienced a 39% decline in breast cancer mortality from 1988 to 2015.[86] A modeling study suggests that two thirds of the decline is due to improvements in

therapy and one third is due to screening.[87] Even with our current screening and treatment technologies a substantial number of women die of breast cancer. This means our current screening and treatment technologies fail a substantial number of women who need effective breast cancer screening and treatment. Efficacy of screening is a function of the character of the disease, the abilities of the screening test, and the effectiveness of treatment. Surveys show that a substantial number of American breast cancer patients get less than optimal care.[88]

Today no major professional organization recommends screening women of average risk before the age of 40 years.[43] There has been much discussion concerning screening women aged 40-49 and whether screening should be yearly or every 2 years.

Newer breast screening technologies

Digital breast tomosynthesis (DBT) or 3D mammography is a relatively new technology.[89] It is FDA-approved as an adjunct to conventional 2D mammography for screening and diagnosis. On average, the test exposes the woman to twice the radiation of conventional mammography. DBT is commonly offered to women undergoing routine screening mammography, but at additional cost because most insurances will not pay for it. This technology shows promise, particularly among women with dense breasts. There are studies that suggest that it can identify more cancers with a lower false-negative rate compared to conventional mammography, but there are no prospective large studies with mortality outcomes to justify its routine use. There is also the concern that the increased sensitivity of 3D mammography may mean more overdiagnosis. The Tomosynthesis Mammographic Imaging Screening Trial or TMIST will enroll 165,000 women 45 years and older, with the Its goal of determining if DBT decreases the incidence of more advanced cancers compared to conventional 2D mammography.

Molecular breast imaging is a fascinating technology that assesses the uptake of a nuclear medicine (a radioactive drug).[90] This test provides an image of the tumor based on cellular metabolism, whereas classic mammography provides an image based on tissue architecture. Molecular breast imaging has tremendous promise since it overcomes some of the density issues of mammography and may be more sensitive for clinically significant tumors vs more indolent overdiagnosis tumors. This technology needs further evaluation.

Today, most experts believe there is some utility to regular mammography. There are also open questions about how often screening should be offered, what age to start, and what age to stop. Breast screening with mammography began after mammography was shown to be a useful diagnostic test. The Health Insurance Plan of New York (HIP) breast screening study would become the first prospective randomized study of a screening technology.[51] Its success and the early diagnosis of several celebrities accelerated the wide dissemination of mammography beginning in the early 1970s. There was a steep learning curve in radiology, pathology, and other medical specialties. To this day, a number of screening centers are experiencing significant patient safety and quality issues. There is still some disagreement among professionals in the diagnosis of breast cancer pathologies. In a recent study in which pathologists reviewed 1 slide from each patient, there was agreement among pathologist for a diagnosis of invasive breast cancer in 96% (95% CI: 94%-97%) of cases. There was agreement in 84% (95% CI: 82%-86%) for ductal carcinoma in situ.[91] There is greater disagreement for diagnosis of atypia.[92]

Colorectal cancer

In May, 1927, Lockhart-Mummery and Dukes published a paper in *Surgery, Gynecology and Obstetrics* entitled, "The Precancerous Changes in the Rectum and Colon."[93] This was an early argument that colorectal cancer begins as a benign polyp. Dukes would go on to demonstrate that patients with lower tumor burden had better survival and establish the first colorectal cancer staging system. There would be debate about the polyp theory until the work of Vogelstein

in 1988 showed that colorectal carcinogenesis was a stepwise process of accumulation of genetic abnormalities, and in 1993 the National Polyp Study demonstrated that the removal of polyps reduced the incidence of colorectal cancer.[94,95]

Gilbertsen began a screening study using rigid sigmoidoscopy in 21,500 subjects at the University of Minnesota in 1948.[96] He demonstrated the colorectal cancer incidence was 85% lower than expected in those screened. He also noted the 5-year survival of those diagnosed with colorectal cancer was 64%, much higher than expected. This result was replicated in 1960, when Hertz and Deddish reported on screening of 26,000 asymptomatic subjects. They found a surprisingly high (90%) 15-year survival in 58 patients diagnosed with colorectal cancer.

Rigid sigmoidoscopy was difficult to do, and the procedure was not widely disseminated beyond several academic facilities.[97] Barium enema often showed additional polyps above the sigmoid colon and this resulted in a high proportion of patients getting colon surgery. Scoping technology improved considerably in the late 1960s and 1970s. Within a short time, the fiberoptic colonoscope could image the entire colon and polypectomy could be performed through the scope.

In the 1930s, physicians realized that occult bleeding was associated with polyps.[97] The chemistry to detect occult blood became practical in the mid 1960s with the introduction of the guaiac card. Screening with the original guaiac test required considerable diet modification. David Greegor, a physician working alone in private practice, demonstrated that guaiac screening followed by diagnostic procedures could find 7 early cancers after he screened 2000 asymptomatic patients.[98]

As the data mounted to show that stool blood testing could lead to the detection of disease, there was legitimate concern: did early detection mean reduction in mortality?[97] Was stool blood testing affected by lead time bias, or length bias? Were the polyps detected and removed never going to progress to cancer? Eight well-designed clinical trials would eventually determine the efficacy of colon cancer screening.

Four prospective randomized trials were launched to assess the efficacy of fecal occult blood testing (FOBT). They were conducted in Minnesota (USA), Nottingham (UK), Funen (Denmark), and Gothenburg (Sweden), with a total of 329,642 average-risk individuals ranging in age from 45 to 80 years at entry.[99-102] Combined results from the 4 randomized trials on FOBT screening showed a statistically significant 16% relative reduction in colorectal cancer mortality rate in the screened group (RR 0.84: 95% CI: 0.78-0.90).[103]

At the same time, 4 prospective randomized trials were launched to assess the efficacy of screening flexible sigmoidoscopy in Norway, the United Kingdom, Italy, and the United States, with a total of 437,600 average-risk individuals ranging in age from 55 to 74 years at entry.[104-107] In the United States, the screening flexible sigmoidoscopy trial was part of the NCI-sponsored PLCO screening trial. In the flexible sigmoidoscopy trials, the summary estimates of reduction in distal colon cancer incidence and colon cancer mortality were 31% (95% CI: 26%-37%) and 46% (95% CI: 33%-57%), respectively.[108]

By the mid 1990s, there was consensus that screening with stool blood tests, sigmoidoscopy, or a combination led to a reduction in cancer incidence and mortality. Stool blood testing technology improved as chemical detection of hemoglobin (the guaiac) yielded to the more specific fecal immunochemical testing (FIT) for human hemoglobin.

Colonoscopy was added to most screening recommendations in 1997.[109] To date, no trials have specifically addressed the efficacy of screening colonoscopy, although patients who tested positive in the fecal occult blood testing trials went on to receive colonoscopy for diagnosis. Within the first 10 years of the University of Minnesota trial, more than 40% of screened participants received a colonoscopy for a positive FOBT. Case series indicate colonoscopy when done well can have a sensitivity of 95% and specificity of 90%. Fecal tests have a sensitivity range of 56%-91% and specificity range of 83%-98% with FIT in the upper ranges. Colonoscopy has been adopted largely based on the above facts; it has not been formally assessed for outcome. It should be stressed that no study has demonstrated colonoscopy screening has less harm compared to other screening. There are complications from colonoscopy and anesthesia for colonoscopy, making formal assessment of outcomes and comparison to sigmoidoscopy and

FIT reasonable. Colorectal cancer screening is undoubtedly a cause of the decline in colorectal cancer incidence and the almost 50% decline in colorectal cancer mortality since 1980.

Newer colorectal screening technologies

CT colonography, also referred to as virtual colonoscopy, is the successor technology to barium enema, using low-dose radiation CT scanning. Comparison of CT colonography to optical colonoscopy has been favorable in terms of identification of early cancers and serious polyps,[110] though there is concern that CT colonography increases radiation exposure. On the other hand, in 1 trial comparing 3000 individuals getting CT colonography and optical colonoscopy, 7 individuals experienced a colonic perforation due to colonoscopy. There were no documented complications due to CT colonography.[110]

Several tests have been marketed to assess various DNA segments associated with colon polyps and colon cancer exfoliated into stool. Most exfoliated DNA tests have been marketed under the "Home Brew Exemption" that does not require FDA approval. One commercial test, Cologuard (Exact Sciences Corporation, Madison, WI) is FDA-approved for screening normal risk individuals.[111] It detects hemoglobin as well as specific DNA segments exfoliated into stool. In a large study, Cologuard had 92% sensitivity in detecting colorectal cancer of any stage (compared to about 74% for FIT). The test had 87% specificity compared to 95% for a leading FIT. There is concern that this lower specificity could lead to too many negative colonoscopies.

A blood test to detect methylated DNA Epi Pro Colon (Polymedco CDP, LLC, Cortlandt Manor, New York) is FDA-approved for screening normal-risk individuals who prefer not to have a stool blood or a scoping procedure.[112] In a study of 149 subjects, the test had a specificity of 99%. Among colorectal cancer patients, it had an 81% sensitivity for individuals with cancer of all stages; it is unclear what the sensitivity is for detection of stage 1 and 2 colorectal cancer.

CT colonoscopy, the FDA-approved stool DNA test (Cologuard), and colon cancer blood test (Epi Pro Colon) have only been assessed to determine that they help find colorectal cancer. They have not been tested in a study with a mortality endpoint. They rely on earlier studies that demonstrate that early detection of colon cancer prevents colorectal cancer deaths. Although a test with a higher sensitivity does not necessarily mean it is more effective in decreasing mortality, a lower sensitivity definitely does not mean the test is better.

Lung cancer

Lung cancer screening using chest radiograph became popular in the United States in the 1960s based on anecdotal reports that chest radiograph screening for tuberculosis control resulted in serendipitous findings of early localized lung cancers. The belief that early detection is always good led the American Cancer Society (and celebrity columnist Dear Abby) to issue public service announcements encouraging Americans to get annual screening chest radiographs.

Four randomized trials to evaluate the efficacy of lung cancer screening in high-risk individuals were conducted in the 1970s. The Memorial Sloan-Kettering and Johns Hopkins trials examined the efficacy of screening with sputum cytology alone, while the Mayo Clinic and Czech trials examined the efficacy of screening with sputum cytology combined with chest radiograph.[113-116] None of these trials demonstrated a benefit to screening. They did show an increase in survival without a decline in mortality (i.e., the consequence of lead time bias). A follow-up of the Mayo trial confirmed the negative result, but also indicated that screening had resulted in overdiagnosis of lung cancer.[117] After long-term follow-up, overdiagnosis was estimated to be 18% of screen-diagnosed lung cancers.

The most recent trial to evaluate the efficacy of chest radiograph screening for lung cancer was the NCI-sponsored PLCO trial, in which 154,901 average risk participants aged 55-74 years were randomized to screening with annual chest radiography vs usual care between the years

1993-2001.[118] After 13 years of follow-up, there was no difference in mortality between the 2 groups (mortality RR 0.99, 95% CI: 0.87-1.22).

Lung cancer screening with CT scanners became feasible as CT computer processors became faster and low radiation dose techniques were developed. Kaneko and colleagues screened 1369 subjects at high risk for lung cancer with both chest radiograph and low dose CT.[119] Fifteen lung cancers were detected with CT, while only 4 were defected by chest radiograph; most were stage 1. Sone and colleagues screened 3958 with low-dose computed tomography (LDCT) and chest radiograph.[120] CT found 19 lung cancers whereas chest radiograph identified 4.

The publication of studies showing that LDCT could find early stage cancer caused a number of American clinics to offer screening. Some institutions put lung screening in their business plan by advertising their lung cancer screening programs and offering screening free or at a discount—this despite the lack of definitive evidence showing LDCT screening to be effective in reducing the risk of death.

Some clinics began pooling data to form a screened cohort. Results of this single arm observational study became a widely cited argument for screening. LDCT was associated with a fairly large number of lung cancers, more than 80% of which were stage 1. The estimated 10-year survival of screen-detected and treated stage 1, nonsmall cell lung cancer patients was 88%. This estimate was widely publicized; largely ignored was the fact that the median follow-up of the cohort was only 50 months, and less than 20% of the subjects were observed for more than 5 years.[121] The biases of screening, especially concerns for overdiagnosis, make it difficult to determine the efficacy of screening from this single arm study.

The National Lung Screening trial (NLST), launched in 2001, is the only prospective randomized trial of lung screening with spiral CT published to date.[122] In this trial, 54,439 individuals aged 55-74 years with a history of at least 30 pack-years of smoking were randomly assigned to either annual LDCT or a single view chest radiograph for 3 years. After approximately 10 years of follow-up, the relative reduction in mortality from lung cancer with LDCT screening was 20% (95% CI: 6.8-26.7; $P = 0.004$). There were 356 lung cancer-related deaths in the screened arm as opposed to 443 in the chest radiograph group. The number needed to screen to prevent 1 death was 320.

The LDCT screening was associated with a reduction in overall mortality. The rate of death from any cause was reduced in the low-dose CT group as compared to the radiography group by 6.7% (95% CI: 1.2-13.6; $P = 0.02$). Screening was most effective among those who were at highest risk, and prevented very few deaths among those at lowest risk. These findings provide empirical support for risk-based screening.

Among those in the screening arm, 43% of those receiving 3 annual screens had a positive test and required additional diagnostic procedures. This most commonly involved conventional CT scans, but in some cases involved needle biopsy, bronchoscopy, mediastinoscopy, or thoracotomy. Ultimately, 96.4% of positive findings were false-positives.[123] Of those having a positive test, 1.4% had a complication from a diagnostic procedure. The NLST reported 16 deaths within 60 days of an invasive diagnostic procedure; it is unknown as to whether the procedure caused the death. It is known that of these 16 participants, 6 did not have cancer. There is increasing interest in evaluation algorithms to decrease the number of invasive diagnostic procedures.

Among those diagnosed with lung cancer in the NLST, 18% were thought to be overdiagnosed.[124] As noted above, analysis of the Mayo Lung Screening study from the 1960s and 1970s also estimated overdiagnosis at 18% of screen detected cancers.[117] An autopsy study of persons dying of other than lung cancer found that 17% had a lung cancer not diagnosed in life.[125]

The radiation exposure of LDCT is small, but it is not insignificant. Cancers associated with lung cancer screening include cancers of the lung, breast, and thyroid. Berrington de Gonzalez estimated the cumulative risk of excess death from lung cancer due to radiation from LDCT screening in 50-year-old smokers to be 2 per 10,000 men screened and 5 per 10,000 women screened. Additionally, an estimated 3 cases of breast cancer per 10,000 women screened may occur.[126]

In September 2018, results from the Dutch Belgian Randomized Lung Screening Trial (NELSON0, were presented at the World Congress on Lung Cancer.[127] As of this publication, the trial results have not been published in the peer reviewed literature. The presentation noted that approximately 15,800 individuals at high risk of lung cancer were randomized to regular screening or routine follow-up over 10 years. Of those participating, 84% were male. There was a 24%-26% reduction in risk of death among men and a 40%-60% reduction among women. Those in the control group were followed through registries. A number of advocates declared that lung cancer screening was proven effective despite the fact the presentation was incomplete. It noted a decrease in lung cancer-specific deaths, but there was no presentation of the harms, especially the number of deaths, associated with interventions due to screening.

The NLST, perhaps more than any other screening test, reveals the double-edged sword of screening. There is a potential for good and a potential for harm. The healthcare professional's challenge is to maximize the good and minimize the harm. Lung screening requires a number of medical specialties. One needs a team with skilled radiology, pulmonology medicine, pathology, medical oncology, radiation oncology, and thoracic surgery specialists. NLST was performed in 30 of the best academic facilities in the United States. An important question involves dissemination of technology. Can these findings be reproduced in other communities in the United States and in other countries? The NLST demonstrates the efficacy (i.e., benefit within the context of a clinical trial) of spiral CT screening, but not the effectiveness (i.e., benefit in the community setting). Will the benefit/harm ratio change with dissemination?

It is estimated that 3.9% of those eligible for lung screening in 2015 received it.[128] This low number is thought to be due to limited access to centers that can offer quality screening and treatment. Many recommendations stress the importance of informing subjects of the potential risks of lung screening. It is unknown how many are offered screening and choose not to get the test. ACS researchers estimate that 8 million Americans are at sufficient risk to qualify for screening. If there was widespread screening and treatment with the quality maintained by the 30 NLST institutions, approximately 12,250 lung cancer deaths could be prevented annually.[129] This is at a cost of perhaps 2200 deaths each year associated with complications due to lung cancer screening and treatment. There are efforts to make screening safer by increasing the size of lesions that should be biopsied and encouraging centers to assess their outcomes.[130]

It has been estimated (by microsimulation modeling) that organized LDCT screening would be cost-effective in Canada, especially when combined with smoking cessation. [125]

Ovarian cancer

Modalities that have been assessed for ovarian cancer screening include the bimanual pelvic examination, serum CA-125 antigen measurement, and transvaginal ultrasound (TVU). The bimanual pelvic examination is highly subjective, and TVU performs poorly.[126]

The serum biomarker CA-125 was developed in the early 1980s by Bast and Knapp.[131] It is FDA-approved to follow the course of diagnosed disease and as a diagnostic test in women suspected of having ovarian cancer. CA-125 is not approved for screening, but some physicians and advocacy groups have promoted screening with it even though there is no study to show screening leads to a decrease in cancer deaths. The comedian Gilda Radner developed ovarian cancer and unfortunately died of it in 1989. Her husband Gene Wilder and Gilda's Club, an organization of ovarian cancer survivors and activists, even sponsored television advertisements encouraging CA-125 screening. This "medical advice" was given before the start of any formal studies of ovarian cancer screening.

Today we know that serum CA-125 is elevated in approximately one half of women with ovarian cancer but can also be elevated in a number of nonmalignant diseases (e.g., diverticulosis, endometriosis, cirrhosis, and uterine fibroids), as well as during normal menstruation and pregnancy. It is neither very sensitive nor specific. [132]

The combination of CA-125 and TVU has been assessed in 2 large, prospective randomized trials. The US trial, the Prostate Lung Colorectal and Ovarian trial (PLCO), enrolled 78,216 women

of average risk aged 55-74 years.[133,134,130] Participants were randomized to receive annual examinations with CA-125 (at entry and then annually for 5 years) and TVU (at entry and then annually for 3 years) (n = 39,105), or usual care (n = 39,111). Participants were followed for a maximum of 13 years, with mortality from ovarian cancer as the main study outcome. At the conclusion of the study, the number of deaths from ovarian cancer was similar in each group. There were 3.1 ovarian cancer deaths per 10,000 women years in the screened group vs 2.6 deaths per 10,000 women years in the control group (RR = 1.18; 95% CI: 0.82-1.71).[134] Of 3285 women with false-positive results, 1080 underwent surgical follow-up; of these, 163 women experienced at least 1 serious complication (15%).[131]

The U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a randomized trial assessing the efficacy of CA125 and TVU in more than 200,000 post-menopausal women.[135] In this trial, 1 arm included serial measurement of CA-125 and used the Risk of Ovarian Cancer Algorithm (ROCA) to determine if diagnostic evaluation was needed. Compared to CA-125 alone, ROCA improved the sensitivity for smaller tumors without measurably increasing the false-positive rate. Primary analysis found a statistically nonsignificant mortality reduction up to 14 years of 15% (95% CI: −3to 30; $P = 0.10$) in the arm using ROCA vs the usual care arm. The reduction in mortality was not constant over time, appearing after 7-10 years of screening. The investigators rightfully suggested that "further follow-up is needed before firm conclusions can be reached on the efficacy of ovarian cancer screening." Despite these findings, the ROCA test is commercially marketed in the United States, and In September 2016, the US FDA issued a press release recommending against its use for ovarian cancer screening.

Today, no medical organization recommends any ovarian cancer screening for women of average risk. An NIH consensus panel did conclude that it might be prudent for women with a known hereditary ovarian cancer syndrome, such as *BRCA1/2* mutations or HNPCC, to have annual rectovaginal pelvic examinations, CA-125 determinations, and TVU until childbearing is completed or at least until age 35, at which time prophylactic bilateral oophorectomy is recommended.[136] This recommendation is based largely on professional opinion. No study has shown a mortality benefit for ovarian cancer screening of high-risk individuals.

In 2015, molecular assessment of a number of tumors that had been diagnosed and treated as ovarian cancer showed evidence that many high-grade serous ovarian cancers are actually tumors of the fallopian tube.[134] Today it is accepted that many, perhaps one half, of the cancers that were called "ovarian cancer" are actually fallopian tube in origin. In the past, some women have undergone bilateral oophorectomy without salpingectomy to reduce risk of ovarian cancer. We now know that the wrong organ was removed in the attempt to reduce their risk of cancer.

Prostate cancer

PSA was first identified by Richard Ablin at Roswell Park in the 1970s.[137] Soon after, it was demonstrated that PSA serum levels are elevated in men with metastatic prostate cancer, and the test was shown to be useful as a diagnostic test and for monitoring the status of metastatic disease. Eventually, case series demonstrated that PSA testing was useful in finding early-stage prostate cancer.[138] At about the same time, the test was approved by the US FDA as a diagnostic tool and to follow the progress of men being treated for prostate cancer. It has yet to be approved for screening asymptomatic men.

In 1993, the American Cancer Society recommended annual serum PSA as a prostate cancer screening test for men age 50 years and older and for African American men age 40 years and older.[139] Americans accepted PSA screening with exuberance. Screening was performed not only in physician offices, but also with mass screening in shopping malls, at state fairs, and even on the floor of the 1994 Republican Convention.[140] Many hospitals and clinics offered free prostate cancer screening. It became a significant profit center for a number of hospitals and clinics, attracting large numbers of men for treatment. There was a significant rise in the number of prostate cancer cases diagnosed, and almost all of those diagnosed received aggressive therapy with radical prostatectomy, radiation, or cryotherapy. As with cervical disease in the 1940s and

1950s, improvements in reducing the side effects of surgery (the nerve sparing radical prostatectomy) made screening and treatment more acceptable.[141]

The recommendation for prostate cancer screening was clearly premature. Although studies showed that screening aided in the diagnosis of prostate cancer, no study showed that screening prevented deaths. It was later published that the widely accepted cutoff for normal of 4 ng/mL was not the result of a formal statistical analysis but a "best guess" after looking at the scatter of PSA data from a screened cohort.[142,143] It is also noteworthy that the first studies to show that treatment of local or regional prostate cancer with external beam radiation and hormones reduced the risk of death were published in 1998.[144,145] The first study to show that radical prostatectomy prevented death was published in 2002.[146] The first prospective randomized study to show that screening might prevent deaths was published in 2009.[147]

The original 1993 American Cancer Society screening recommendation was highly controversial among screening experts. In 1997, the ACS adopted the first recommendation to stress informed decision making.[109,148] That is, the patient should be encouraged to decide regarding screening after being informed of the potential risks and potential benefits of screening.

A drop in prostate cancer-specific mortality occurred simultaneously with the introduction of screening and the rise in incidence. The initial decline was most likely due to improvements in the treatment of metastatic disease.[149] There is some speculation that the decline is due to a change in attribution of cause of death, a slippery-linkage bias. Several prostate cancer therapies that became widely available at that time are now known to increase the risk of death from cardiac disease.[150,151] Although the decline in mortality started too early to be entirely due to screening, some of the mortality drop, a decade or so after screening began, is very likely due to screening and treatment of localized disease. Unlike with breast cancer, there is a decline in the population incidence of metastatic disease at diagnosis that parallels the use of—and is therefore likely due to—PSA screening.[152]

Several prospective randomized trials to evaluate prostate cancer screening started after the surge in screening within the US population, including the PLCO screening trial conducted in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC).[153]

The PLCO randomized more than 70,000 men age 50 years and older to annual screening or no screening. The trial demonstrated an increase in prostate cancer incidence with screening (RR 1.12; 95% CI: 1.07-1.17) but no reduction in prostate cancer-specific mortality after 13 years of follow-up (RR, 1.09: 95% CI: 0.87-1.36).[154] PLCO was conducted in American clinics at a time in which PSA screening was already thought to be beneficial and was very popular. It was compromised by the screening excitement. There was difficulty in maintaining minimal use of PSA screening in the control group. This was less of a problem in Europe, where screening had not met the enthusiasm seen in the United States.

The ERSPC was a multicenter trial.[155] It might best be thought of as a meta-analysis of 7 screening trials involving more than 180,000 men, age 50-74 years, in 7 countries. Each trial differed slightly in PSA cutoff and the screening schedule. There is some suggestion that treatment options varied as well. The 7 trials of the ERSPC, assessed together, demonstrated an increase in cancer incidence with screening (RR 1.63; 95% CI: 1.57-1.69). The trial failed to show a benefit among the entire study population. However, a predefined cohort of 162,000 men aged 55-74 years had a 21% reduction in prostate cancer-specific mortality after 11 years of follow-up (RR 0.79, 95% CI: 0.68-0.91).

Importantly, there are major discrepancies in the results from the different components of the ERSPC trial. Screening was very effective in the Swedish component.[154] It also reduced mortality in the Netherlands, but this finding was just barely statistically significant. There was not a statistically significant reduction in mortality among patients in the 5 other countries. Most importantly, screening did not yield a statistically significant reduction in deaths in Finland, the largest of the 7 trials.[156,157] These discrepancies have so far not been explained. There is some indication of differences in quality of treatment available between the 2 arms of the trial, especially in the Dutch study.[156] This is a bias that could have contributed to the apparent beneficial

effect in the Netherlands. As is common in Sweden, the Swedish trial randomized men in such a way that those in the control arm were not aware that they were in the trial.[154] Such designs can appear to increase screening effect because deaths in the control arm may not be counted completely.

The ERSPC finding is consistent with 1 prostate death being prevented for every 1000 men, ages 55-69 years, screened over 13 years. If one were to look at the Swedish data only, the benefit to harm ratio would be better. If one were to look at only the Finnish data, the benefit to harm ratio would be worse.

The ASCO explanation of screening benefits is perhaps the easiest for men to understand.[158] Given 1000 men who choose to be screened over more than a decade, 96 will be diagnosed with prostate cancer. Given 1000 men who choose not be screened, 60 will be diagnosed with prostate cancer of the 1000 men who choose to be screened over more than a decade, 4 will die of prostate cancer. And finally of the 1000 men who choose not to be screened 5 will die of prostate cancer.

The 4 deaths out of 1000 men vs 5 deaths out of 1000 men represents the 20% reduction in relative risk of death.

A decade ago, almost all men with localized disease were treated aggressively. Today, an increasing number of prostate cancer patients are being watched as initial treatment. In 2018, The American Urological Association, American Society for Therapeutic Radiation Oncology, and the Society for Urologic Oncology issued a joint statement declaring the preferred treatment of early stage low risk prostate cancer is observation.[159,160]

The United States had an epidemic of prostate cancer screening and treatment beginning in the early 1990s. This was due to the hope that early detection and treatment was beneficial. Today there is consensus that a small number of men benefit from prostate cancer screening, but a substantial number of men diagnosed with prostate cancer will be victims of overdiagnosis and are subject to overtreatment, unless they are carefully observed before proceeding to prostatectomy or radiation therapy, a process called “watchful surveillance.”[161] Most expert groups that have examined the prostate screening data recommend informed decision making regarding the benefits and risks of screening to include the possibility of diagnosis and being observed rather than receiving definitive treatment. It is fair to say that the change away from a rush to aggressive treatment has changed the calculus on which a decision to be screened is based.[161]

Neuroblastoma

Neuroblastoma is a common pediatric cancer. Neuroblastoma commonly excretes metabolites of norepinephrine and dopamine. Measurement of urine vanillylmandelic acid, and homovanillic acid has been used to screen for this disease. Screening was never common in the United States, but became popular in Japan and parts of Canada. Four large studies from Japan, Canada, and Europe screened more than 10 million children at age 6 months to 1 year of age. In ecologic study, the incidence of neuroblastoma was compared with historic controls and unscreened children from the same country.[162-165]

All studies had similar findings. Screening led to the diagnosis of more neuroblastomas; and they were overwhelmingly low-stage tumors with favorable biologic features. There was no decrease in the incidence of high-risk tumors in children over the age of 1 year. Finally, mortality did not decline in the screened populations.

Neuroblastoma is also a disease very prone to overdiagnosis. Many early-stage neuroblastomas seem to undergo spontaneous regression and would not be diagnosed without screening. In a study in which 22 patients with screen-detected neuroblastoma were observed and treated at evidence of progression, spontaneous regression occurred in 13 (59%). Expectant observation of screen-detected tumors appears safe and reduces the risk of surgical morbidity.[166]

Thyroid cancer

There are no formal recommendations for thyroid cancer screening in the United States; however, the wide availability of ultrasound technology has made it easy to assess the thyroid. This has led to a tripling of thyroid cancer incidence in American women over the past 3 decades. Female thyroid cancer mortality has remained static during this period. Thyroid screening became common in the Republic of Korea (South Korea) in the 1990s. As a result, the 2011 age-adjusted thyroid cancer incidence rate was 15 times the rate in 1993. Mortality rates, again, remained static.[167] This observation is evidence of overdiagnosis. The availability of imaging technology has made it easier to overdiagnose thyroid cancer. Treatment protocols at many major centers now call for observation of small thyroid cancer lesions.[168]

Oral cancer

Routine mouth examination has been advocated for individuals at high risk of head and cancer. Several organized screening programs have demonstrated that a number of cancers can be diagnosed. The Oral Cancer Case Find Program used well trained health care providers to screen more than 10 million patients over 8 years. More than 3200 premalignant lesions and more than 700 cancers were found.[169] A cluster randomized trial in India examined the efficacy of oral cancer screening at 3-year intervals utilizing visual inspection, and found no benefit to screening (RR 0.88, 95% CI: 0.69-1.12).[170,171] It is noteworthy that 37.5% (1927 of 5145) of individuals with a positive screen did not comply with follow-up referral. Taken together, these studies suggest that screening for head and neck cancer using physical examination might be beneficial. Oral examination is very subjective. Future strategies might use more objective methods such as detection of molecular abnormalities in saliva. These methods must be subjected to rigorous clinical trials.

Liver cancer

The mortality rate from liver cancer has increased 40% over the past 2 decades.[172] This has led to increasing pressures to screen individuals at high risk due to viral hepatitis, cirrhosis, and fatty liver disease. Observational studies suggest that regular surveillance of those at high risk for liver cancer reduces the stage at diagnosis and increases survival.[173,174] Findings from observational studies can be prone to the effects of lead time length bias. One randomized trial of 19,200 patients with chronic hepatitis B virus (HBV) infection assessing surveillance every 6 month with alpha fetoprotein and ultrasound found a 37% reduction in hepatocellular carcinoma (HCC) specific mortality.[175] A second randomized trial to confirm this finding or extend the question to those at high risk due to other than hepatitis B is unlikely.

Screening: the future

Virtually every screening test in use today began as a diagnostic test. Today there are diagnostic tests to detect proteins, tumor cells, nucleic acids, epigenetic markers, or other biomarkers for cancer in the blood. Their potential as screening tests are being discussed especially in asymptomatic subjects at high risk for a particular cancer.

As technologies improve it is imperative that medicine return to basic principles and carefully assess a screening test before widely implementing it. Time and time again, medicine has adopted a screening test without adequate assessment and harm has resulted. In general, the strength of evidence from strongest to weakest comes from: (1) prospective randomized trials (blinded, unblinded); (2) non-randomized, controlled, clinical trials; and (3) case series or other

observational study designs (population-based, consecutive series, consecutive cases, nonconsecutive cases or other observational study designs [e.g., cohort or case-control studies]).

Prospective randomized trials are time consuming, expensive, and difficult to conduct, but they are the gold standard for demonstrating the risks and benefits of a screening test. The harms associated with screening should be assessed in addition to the disease-specific and overall mortality. Most screening tests are only powered to assess disease-specific mortality. Powering for overall mortality is preferable but often too expensive.

Interesting technologies that could become screening tests include a test for circulating tumor DNA (ctDNA). Such a test has been useful in detecting minimal residual disease in stage 2 colorectal cancer patients and for predicting those who are destined to relapse and need adjuvant therapy.[176] Tests to measure circulating tumor DNA have also been used as an early indicator of chemotherapy response in patients with metastatic colorectal cancer. A similar approach is being used in the development of tests for markers in body fluids other than blood. A test to detect DNA released from ovarian and uterine cancer into uterine, cervical, and vaginal fluids is being studied as a diagnostic test, and could eventually become a screening test. The same cervical fluids used to test for human papilloma virus (HPV) can possibly be tested for evidence of uterine or ovarian cancer. Somatic mutations detected in saliva may indicate the presence of head and neck cancer, and mutations of DNA in urine may indicate bladder or prostate cancer.

Most available tests have relatively low sensitivity for detection of early stage cancer. Increasingly, combinations of tests are being assessed to improve operating characteristics. Tests in development detect combinations of: somatic DNA mutations, changes in DNA methylation, cancer specific mRNA, cancer specific proteins, and cancer specific metabolites.

The liquid biopsy and other new tests show great promise, but there are concerns. Some might potentially detect the presence of an early cancer but be unable to specify the organ site and potential treatment.[94] A false-positive could lead to significant emotional stress and potentially harmful and unnecessary diagnostic testing.

Conclusion

Time and time again, physicians have become fascinated with the idea of early detection, forgotten the basic principles of screening, and disseminated a technology before adequate assessment. In the case of cervical, breast, lung, ovarian, prostate, and even colon cancer screening, some people were seriously harmed as screening led to unnecessary diagnostic procedures and unnecessary treatment.

Perhaps we can go forth developing the new generation of screening tests with wisdom. That is, with the knowledge of earlier experiences. We must remember the principles of cancer screening and past mistakes. Technology can advance quickly, but our ability to analyze the impact of that technology, and determine how best to use it, takes more time and patience. It is clear that a screening test should be proven effective in reducing mortality in randomized controlled trials before being widely implemented. Effectiveness involves an assessment and a balancing of both the benefits and harms of the intervention. These randomized controlled trials should employ carefully predefined age groups or risk cohorts. Once a screening test is proven effective, it should be used in programs in which there is an ongoing quality control program and the screened population should be monitored for outcomes. The effectiveness of a screening test should be monitored, as use of the test may need to be modified or even withdrawn from use if found to be ineffective.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1067/j.cpsurg.2018.12.006.

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