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EARLY CANCER DETECTION: CURRENT STATUS AND EMERGING STRATEGIES

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РАННЯЯ ДИАГНОСТИКА РАКА: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ И НОВЫЕ СТРАТЕГИИ

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В связи с высокой заболеваемостью, высокой стоимостью лечения и самой высокой смертностью среди неинфекционных болезней рак остается одной из основных проблем здравоохранения во всем мире. По данным Globocan в 2012 году в мире выявлено 14,1 миллиона случаев заболевания раком, при этом 8,2 миллиона человек погибли от различных злокачественных опухолей. На долю стран с низким и средним уровнем доходов приходится 57% (8 миллионов) заболевших, в то время как смертность в этих странах составляет 65% (5,3 миллиона). Ранняя диагностика злокачественных опухолей играет важную роль для улучшения результатов лечения онкологических больных, снижения стоимости терапии и сокращения онкологической смертности. Тем не менее, влияние программ ранней диагностики рака на выживаемость пациентов остается спорным, что связано с ограничениями чувствительности и специфичности существующих скрининговых тестов. В частности, скрининговые программы показали свою эффективность для ранней диагностики рака молочной железы, шейки матки и толстого кишечника, в то время как гипердиагностика при раке предстательной железы вызывает определенное беспокойство. В связи с этим поиск новых биомаркеров и методов ранней визуализации опухолей остается предметом интенсивных исследований и дискуссий. В статье освещаются текущее состояние проблемы и основные достижения в области скрининга рака.

Ключевые слова: ранняя диагностика рака, скрининг рака, рак молочных желез, маммография, термография молочных желез, лучевая диагностика рака, биомаркеры рака, рак легкого.

Cancer is a major public health problem because of its high incidence, the highest mortality, among other non-communicable diseases in the world and the burden costs. Globocan 2012 reported 14.1 million new cancer cases and 8.2 million cancer deaths worldwide. 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% occurred in low- and middle-income countries. Therefore, early cancer detection is critical for improving patient outcome, cost effectiveness of treatment, and decrease mortality rate. However, the benefit of early detection of cancer on patient survival is still controversial because the limitation in both sensitivity and specificity of the current screening tests. Thus, patients with few cancer types have been benefited from screening tests. The role of cancer screening has been established in breast, cervical and colon cancer, but in prostate cancer, overdiagnosis is a concern.

The role of novel biomarkers and imaging screening in the early diagnosis of cancer are a subject of intensive research and a matter of debate. This article highlights the current status and the main advances in cancer screening.

Keywords: early cancer detection, cancer screening, breast cancer, mammography, breast thermography, cancer imaging, cancer biomarkers, lung cancer.

1. The role of Imaging in Breast Cancer Screening

Mammography is the only screening test proven to reduce mortality and, is the "gold standard" for breast cancer screening. Mammography screening in women older than 50 years improves survival by 20%–25%. Overall, mammography reduces the breast cancer mortality by 19%. The most benefited group is women in their 60s with a reduction from breast cancer mortality of 32%, while the reduction in women in their 40s is 15% [1–6]. However, the main disadvantages of this technology are reduced sensitivity in younger women/ dense breasts and in high-risk subpopulations. Moreover, mammography has a high rate of false positives, excessive biopsies, increase cost, and patient anxiety.

Advances in mammography have included the incorporation of new technologies as Digital Mammography. Digital Breast Tomosynthesis (DBT) and Contrast Enhanced Spectral Mammography (CESM). While analog mammography sensitivity in women with dense breasts ranges from 30% to 50%, digital mammography increases sensitivity in dense breasts from 55% to 70%. However, an increase in overall cancer detection has not been reached with digital mammography [6].

Concerns regarding the radiation risks from mammography lead to the development and FDA approval of Spectral imaging or photon-counting full-field digital mammography with an acceptable image quality [7].

Automated Breast Density.

Because of the limited sensitivity of mammography in women with dense breast, the calculation of breast density, is possible by using a software with an algorithm that utilizes volumetric parameters, that can be integrated into a personalized breast cancer risk assessment. This software can be incorporated in to the mammography work. However, at present time there is no agreement among radiologists and this information is not integrated yet in the clinic [8–10].

Digital Breast Tomosynthesis (DBT).

DBT produces tomographic "slices", similar to a CT scan, using a single acquisition and eliminates overlapping breast tissue in digital mammography, a frequent cause of false positive cases. Therefore, DBT can increase specificity in mammographically detected masses. DBT decreases recall rates on screening mammography, ranging from 39 to 41% and reduce false negative examinations due to dense breast tissue [6]. However, the main limitation are a decreased sensitivity for detection of microcalcifications, requires more radiation dose, approximately 8% higher than digital mammography [11], and increase the time to read.

Contrast Enhanced Spectral Mammography (CESM).

CESM requires an injection of an iodinated contrast agent. This technology can image blood flow in breast masses using temporal subtraction and dual energy subtraction [12-15]. CESM in combination with ultrasound and digital mammography increases sensitivity from 78%–92%. CESM detection index is 96% comparable to MRI, while digital mammography is 85%. CESM lesion specificity is 100% superior to MRI (81%) [6]. This technology has not been evaluated in the setting of breast cancer screening but is currently under evaluation as a diagnostic tool.

In summary, both DBT and CEST have been approved by FDA in addition to digital mammography and had improved sensitivity and specificity, but their role in breast cancer screening has not been defined.

Magnetic Resonance Imaging (MRI).

MRI is recommended for women at high-risk for breast cancer as outlined in Table 1 summarizing American Cancer Society Recommendations for Annual Supplemental MRI Screening.

Table 1

American Cancer Society Recommendations for Annual Supplemental MRI Screening

a.) High Risk women for whom annual MRI is recommended

BRCA1 or BRCA2 gene mutations

First-degree relative with BRCA1 or BRCA2 mutation who have not been tested

Lifetime risk of breast cancer or 20–25%

History of radiation therapy to the chest between the ages of 10–30 years

Li-Fraumeni, Cowden or Bannayan-Riley-Ruvalcaba syndrome

b.) Women at Moderately Increased Risk who Should Talk to their Doctors About the Benefits and Limitations of MRI screening as an Adjunct to Mammography

Lifetime risk of breast cancer of 15–20%

Personal history of breast cancer ductal carcinoma in situ

History of lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia at biopsy

Extremely dense or unevenly dense breasts

MRI is the most sensitive technique for breast cancer detection (95%) and has superior sensitivity to mammography and ultrasound in the detection of invasive cancer. 14.7 cancers per 1000 women detected when MRI is used as additional to mammography and whole breast ultrasound [6, 16]. However, its decreased specificity is controversial because biopsy of follow up imaging is frequent after a MRI study. Moreover a reduction in mortality from breast cancer as a result of MRI screening, has not been demonstrated.

Breast Thermography (BT).

Most of the current and newest imaging modalities for early cancer detection, although promising, are too expensive for routine use. Breast cancer in developed and developing countries requires new strategies to increase early detection and access to care. Clinical thermography is a non-invasive, non-contact and non-ionizing radiation imaging technique that detects, records, and forms an image of the temperature distribution on the surface of the body. In the 1960s and early 1970s, BT was actively evaluated as a feasible screening tool for early breast cancer detection. However, the negative results showing high false-positive rates and low sensitivity, and reported in 1979 by the Breast Cancer Detection and Demonstration Project [17], decreased interest in BT . Although BT was approved by the FDA in 1982 for use as an adjunctive breast cancer screening procedure, this diagnostic approach was abandoned [18]. Since 2006 our group is evaluating BT as screening for early detection of breast cancer. Preliminary results, showing comparable results with conventional mammography were presented at 2009 ASCO Annual Meeting [19]. From November 2006 to December 2014, 4208 women were screened. 2907 (69%) of them were 40 years and older and 1301 (31%) were women 25–39 years old. With a median follow-up of 5 years (Range 1–10 years), 15 (0.5%) women older 40 years old and 4 (0.3%) younger women were diagnosed as having breast cancer after one to 5 years of BT screening. Only 3 out 19 (16%) women were diagnosed with cancer one year after BT screening and the remaining 16 patients between 3 and 5 years. Sensitivity and specificity were 94% and 85%, respectively. The results of our series showed that BT is a feasible tool for breast cancer screening. Moreover, the incorporation of both image processing techniques and smart processing approaches, also known as artificial intelligence, will help to reduce the false-positive diagnosis rate, and avoid bias associated with physician analysis of BT images. Our group had developed a software with an algorithm that utilizes clinical characteristics and infrared imaging, with the aim to develop a personalized breast cancer risk assessment. This software is under evaluation.

2. The role of Biomarkers in early cancer detection

Testing for the right biological molecules, whose presence indicates cancer, could increase survival rates more than current screening tests such as mammography. However, up to date, few useful blood-based biomarkers had showed a potencial ability for early cancer detection.

Circulating tumor cells (CTCs) and cancer-specific (mutated) cell-free, circulating tumor DNA (ctDNA) are one of the most promising biomarkers for the early diagnoses of cancer. Both techniques can be used either as a dynamic prognostic biomarker or as tumor material for “liquid biopsy”. Breast cancer appears is the cancer type in which CTC have been the most extensively studied supporting the clinical validity of CTC. There are a number of limitations, such as lack of standardized methodologies and reference standards for use in DNA methylation detection, to overcome before such biomarkers will be validated in clinical trials. Despite the potential role in cancer screening of both techniques as reviewed in detail by Schiffman [1] and others [20,21], is too early to establish a useful role en early cancer detection. In conclusión, currently there are no blood-based biomarkers suitable for population screening or early diagnosis of cancer, because the majority still fail the initial phases of the biomarker evaluation process [22].

3. Lung Cancer Imaging

Lung cancer is the most common cancer in the world, its incidence and mortality rates are 12.7% and 18.2% per year, respectively. It is generally diagnosed in its late stages, when prognosis is poor. 80% of patients with lung cancer died during first five years of diagnosis. Lung cancer screening includes the use of low-dose computed tomography (CT) scans, focused on high-risk groups such as smokers and people with preexisting lung disease. The National Lung Screening Trial (NLST), the largest randomized clinical trial demostrated a 20% reduction in death in current or former smokers.

Annual screening is recommended for high-risk individuals who are 55 to 80-year-olds and with a history of heavy smoking. However, the harms are not well enough understood [23–26].

Conclusions

Despite there are no new tissue types or blood/urine/salive – based biomarkers or new imaging techniques validated in clinical trials that can be incorporated for cancer screening or into the clinic, the field of early cancer detection is a subject of intensive and active research. In order to improve survival rates, advances in the knowledge of cancer biology, cancer development and progression, through continued research, are needed for the developing of new imaging technologies and more accurate biomarkers.

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