SCIENTIFIC REVIEWS

Improving Early Cancer Diagnosis by Artificial Intelligence Algorithms and Machine Learning Models

AthanasiosValavanidis
Department of Chemistry, National and Kapodistrian University of Athens, University Campus Zogrtafou, 15784 Athens, Greece
E-mail : Valavanidis@chem.uoa.gr

Abstract

Cancer is one of the most important global health problem. The *Global Burden of Disease* estimated that 9.56 million people died prematurely as a result of cancer in 2017. Medical professionals agree that improvements in the application of prevention and lifestyle changes (diet, smoking, obesity) and early diagnostic detection can reduce substantially incidence and mortality from most types of cancer, while increasing better treatment with less cost and better quality of life for cancer patients. In the last decade, many diagnostic tests and methods have been improved with higher accuracy. Tests are subdivided into Imaging (Radiology) tests, endoscopy procedures and biopsy and cytology tests. These diagnostic tests inevitably produce vast amounts of data which need to be examined by experts and to differentiate between benign and malignant tumours. Now Artificial Intelligence (AI) applications can be used to examine large numbers of diagnostic imaging with improved accuracy amplifying the efficiency of the health system. New technological advancements in AI algorithms and improvements in computer hardware can be used to train artificial neural networks to acquire diagnostic experience from large number of scans. Already some deep learning and machine learning models can teach computers to compare and analyze enormous amount of scanning data for cancer. The diagnostic skills of highly sophisticated software have been tested and compared with the traditional diagnostic tools by cancer experts. Their accuracy is much improved and are considered very helpful in early diagnosis as well as prognosis of the extend of various cancers. Scientists turned into artificial intelligence (AI) systems that are capable of surpassing human experts in breast cancer prediction and much earlier diagnosis. Similarly, computer scientists devised AI algorithm and deep learning models that could predict which people would go on to develop lung cancer by analysing low-dose CT (computerized tomography) scans of the lungs. Recently, application of convolutional neural network (CNNs) was used in the diagnosis of the invasion depth of gastric cancer based on conventional endoscopy. Also, studies demonstrated that AI approaches combined with imaging can have considerable impact on early diagnosis of oral cancer outcomes, with algorithm-guided detection of oral lesion heterogeneity. This review collected some very interesting research papers on the subject

Introduction: Global cancer, incident and mortality

Cancer is the second most important cause of morbidity and mortality (after cardiovascular diseases) and the world's most challenging health problem. Cancer mortality and morbidity statistics for individual countries is an important indicator for organizational aspects of health systems worldwide. The most comprehensive and observational epidemiological report *Global Burden of Disease* estimated that 9.56 million people died prematurely as a result of cancer in 2017. Cancer incidence and mortality are rapidly growing worldwide. The reasons are complex but reflect both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic developments, lifestyle practices and exposure to carcinogenic factors (smoking, diet, obesity, exposure to sunlight, lifestyle, etc).[1,2]

The **Global Burden of Disease Study** (**GBD**) began in 1990 as a study commissioned by the World Bank and approved by the World Health Organization (WHO). The report also introduced the **disability-adjusted life year** (**DALY**) as a new important metric to quantify the burden of diseases, injuries, and risk factors in various countries. The report is a comprehensive regional and global observational epideiological research programme that is supported by the collaboration of over 1,800 researchers from 127 countries, conducted under the principal investigator Prof. C.J.L. Murray, based out of the Institute for Health Metrics and Evaluation (IHME) at the University of Washington (USA), funded by the Bill and Melinda Gates Foundation. [https://www.who.int/healthinfo/global_burden_disease/about/en/].

Statistical evidence in 2018 worldwide recorded more than 18 million new cases of cancer (called incidence). From the 18 million, 5 million were cases of breast, cervical, colorectal and oral cancers that could have been prevented or treated in better ways if detected much earlier. All scientific studies in various countries showed that early detection, better screening and correct diagnosis of the type and extend of cancer, could have been significantly improve cancer patient survival rates, better treatment, better quality of life as patients and in addition would have significantly reduce the cost and complexity of cancer medical treatment. By addressing the early cancer detection, government health systems, the private health sector and cancer patients would have reduced the financial burden of cancer not only in individual countries but also on a global scale.[3,4]

Worldwide, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing close to 1 in 5 (18.4%)of cancer deaths. Smoking and air pollution in cities are the leading causes of lung cancer.[5,6]

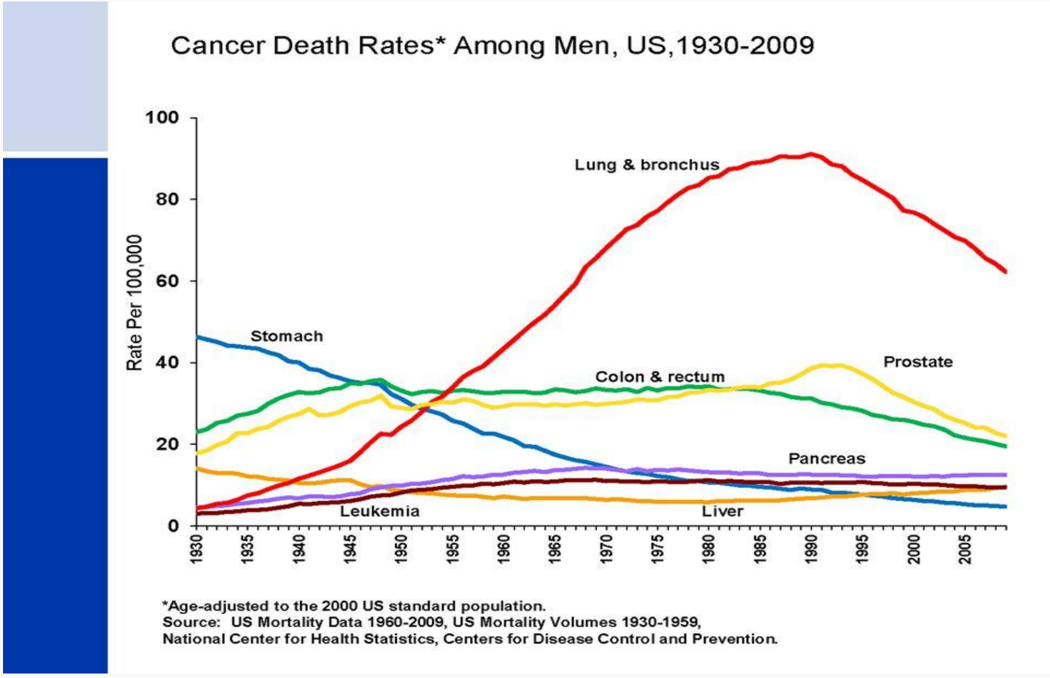

Figure 1. National Center for Health Statistics, CDC and Prevention, USA. Cancer death rates for men in the USA 1930-2009, age-adjusted to the 2000 US standard population. Notice, that Stomach cancer drops substantially because of refrigeration and better diet. Lung and bronchus cancer increased exponentially because of smoking habits. Other cancers remain almost at the same level. Lung cancer is by far the most common cancer in men (28%), followed by prostate (10%), and colon & rectum (9%).

The USA is a developed country with advanced industry and services, representing a typical western society in terms of diet, smoking habits and lifestyle. Also, USA has some of the best medical statistical agencies for morbidity and mortality. The National Cancer Institute (NCI) of the USA reported 1,7 million new cases of cancer in 2018 (incidence, age-adjusted to a standard population). In 2018, nearly 50% of all new cancer cases were expected to be the most prominent types of cancers, such as prostate, female breast, lung, and colon/rectum. Also, according to American Cancer Society projections, about 1,735,350 new cases of cancer are expected to be diagnosed in 2018, including 164,690 cases of prostate cancer, 266,120 cases of female breast cancer, 234,030 cases of lung and bronchus cancer, and 140,250 cases of colon and rectum cancer. [National Cancer Insitute, *Cancer Trends Annual Progress Report*, February 2019, https://progressreport.cancer.gov/diagnosis/incidence]. Statistical evidence from the USA (NCI) showed that in 2020, 1,806,590 new cancer cases and 606,520 cancer deaths are expected.[7]

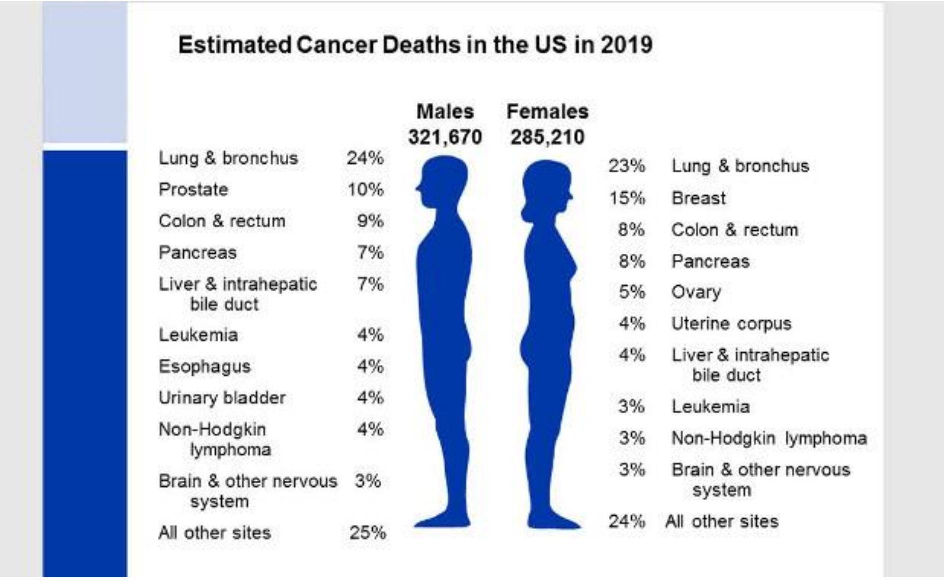

Figure 2. Statistical evidence in the USA shows a steady, 25-year decline resulted in a 27% drop in the overall cancer death rate in the U.S., translating to approximately 2.6 million fewer cancer deaths between 1991 and 2016. The data come from **Cancer Statistics, 2019**, the American Cancer Society's. The report estimates that in 2019, 1,762,450 new cancer cases and 606,880 cancer deaths will occur in the U.S. Since its peak of 215.1 deaths (per 100,000 population) in 1991, the U.S. cancer death rate has dropped steadily by approximately 1.5% per year to an overall decline of 27%. This translates to an estimated 2,629,200 fewer cancer deaths than would have occurred if mortality rates had remained at their peak. Cancer is the only leading cause of death with continuous sustained declines over the past 25 years. The decline in cancer mortality over the past two decades is primarily the result of **steady reductions in smoking and advances in early detection and treatment**, which are reflected in the declines for the four major cancers: lung, breast, prostate, and colorectal.

*Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. J: *A Cancer J Clinicians,* 69(1):7-34, 2019. https://doi.org/10.3322/caac.21551.

Prevention and early diagnosis of cancer cases

Prevention of cancer can be achieved by changing lifestyle behaviour (e.g. smoking, diet, obesity), reduction of exposures to carcinogenic substances and agents (sunlight, asbestos fibres, polycyclic aromatic hydrocarbons, air pollution, etc) and applying early-detection strategies (e.g. improved screening methods, chest x-rays, breast mammography, etc) to detect cancer at the early stages. Preventative measures and early diagnosis tests have great potential to reduce the population burden of cancer. It has been estimated that 50% to 60% of cancers could be prevented if known health strategies were optimally used.[8,9]

Medical professionals agree that improvements in the application of prevention and early detection can be optimized, but that additional prevention and early-detection strategies can still be developed. According to WHO detecting most types of cancer early can effectively reduce the mortality associated with cancer. In resource-poor settings, cancer is often diagnosed at a late-stage of disease resulting in lower survival and potentially greater morbidity and higher costs of medical treatment. Even in countries with strong health systems and services, many cancer cases are diagnosed at a late-stage. Addressing delays in cancer diagnosis and inaccessible treatment is therefore critical in all settings for cancer control. Early diagnosis strategies improve cancer outcomes by providing adeqaute health care at the earliest possible stage and are therefore an important public health strategy in all settings.[10]

Tests to find and diagnose Cancer have been developed over the years and with improved accuracy. TestS are subdivided into 3 sections: Imaging (Radiology) tests, Endoscopy procedures and Biopsy and Cytology tests. [11]

a. **Imaging (Radiology) Tests**. Imaging tests for cancer detection is to make pictures (images) of the inside of the human body to find out how far malignant (cancerous) growths have spread, and to help determine if cancer treatment is working. CT Scans (computer tomography), MRI (Magnetic Resonance Imaging), X-rays and Other Radiographic Tests, Ultrasound, Nuclear Medicine Scans and Mammograms.

Magnetic Resonance Imaging (MRI) for breast cancer

b. **Endoscopy Procedures.** Endoscopy is a medical procedure where a doctor puts a tube-like instrument into the body to look inside for malignant tumours. Bronchoscopy, Colonoscopy, Cystoscopy, Laparoscopy, Laryngoscopy, Mediastinoscopy, Thoracoscopy, Upper Endoscopy.

c. **Biopsy Tests for cancer (**Fine needle biopsy, Core needle biopsy, excisional biopsy, endoscopic, laparoscopic, thoracoscopic, etc). **Cytology Specimens** for cancer (Fine needle aspiration, Spinal fluid**,** also known as *cerebrospinal fluid,* Pleural fluid from the space around the lungs, etc).

These diagnostic tests can be used at an early stage of a cancer and can save lives.[11] It must be emphasized that if a cancer is diagnosed at an early stage and hasn't spread (metastasis) or has been a large malignant growth, it can be treated successfully and improve survival by 5-10 years at a reduced costs and less painful treatment of cancer patients. [12]

Early diagnosis has improved substantially for the following types of cancer: **bowel cancer**, if diagnosed at the earliest stage, more than 9 in 10 bowel cancer patients will survive. **Breast cancer**, more than 90% of women diagnosed at the earliest stage will survive for at least 5 years compared to ~5% for women diagnosed at an advanced stage. **Ovarian cancer**, diagnosis at an earlier stage can save 90% of women for at least 5 years survival, compared to only 5% for women diagnosed at later stage. **Lung cancer**, the most deadly cancer (especially in men smokers) can be reduced if diagnosed at an early stage. More than 80% of lung cancer patients will survive at least a year if diagnosed at an early stage.[13]

Artificial Intelligence (AI) applications in medical practice

Artificial intelligence (AI) and machine learning have been used for many decades at various forms. Applications of AI have brought major changes in communication, transportation, media and medical applications. In the last decade AI has also begun to be incorporated into medicine to improve patient care by speeding up processes and achieving greater accuracy, opening the path to providing better healthcare overall. Artificial intelligence algorithms and machine learning models can be used to help in the process of diagnosis and treatment of patients and augmenting physicians' capabilities. Generally, an algorithm takes some input and uses mathematics and logic to produce the output. In stark contrast, an AI algorithm takes a combination of both – inputs and outputs simultaneously in order to "learn" the data and produce outputs when given new inputs. This process of making machines learn from data is what we call machine learning**.**

New developments in Artificial Intelligence (AI) is poised to revolutionize and transform medical practice with various automated technologies in the diagnosis, treatment and prediction of outcomes among patients. Most physicians spent much more time performing data entry and desk work during the office consultation than actually talking to patients.[14,15]

Although diagnosis and treatment seem simple on many occasions, they require extensive professional background, knowledge and logical thinking. AI can help in the collection of patients' data, physical examinations, and laboratory tests. Also, AI can examine and interpret collected data and medical results, provide diagnosis based on collected health related information and matching it with previous information and knowledge, Finally, AI can select appropriate treatment plans from the diagnosis and administer to patients, while re-evaluating the diagnosis and treatments. In this respect AI may do better than doctors in many ways, but increased use of AI could raise certain ethical dilemmas and bring about many issues of concern. The diagnostic skills of highly sophisticated software have been tested and compared with the traditional diagnostic tools and experts, and found very helpful in diagnosis as well as early prognosis of various disease.[16,17]

Improving early diagnosis by AI in mammography of breast cancer

Despite recent advances in breast ultrasound and magnetic resonance imaging (MRI), screening mammography has been established for many years to identify breast cancer at earlier stages of the disease, when treatment can be more successful with saving lives. Mammography screening programs for breast cancer have been criticized due to the high recall rate and high rate of false-positives resulting in unnecessary biopsies. Despite the existence of screening programmes worldwide, the interpretation of mammograms is affected by high rates of false positives and false negatives. Scientist turned into artificial intelligence (AI) systems that are capable of surpassing human experts in breast cancer prediction. Recent large representative datasets from the UK and a large enriched dataset from the USA were used. The study showed an absolute reduction of 5.7% and 1.2% (USA and UK) in false positives and 9.4% and 2.7% in false negatives. In an independent study of six radiologists, the AI system outperformed all of the human readers. Artificial intelligence (AI) is capable of advanced learning using large complex datasets and has the potential to perform tasks such as image interpretation. With both highly-specific capabilities, and also possible un-intended (and poorly understood) consequences, this viewpoint considers the promise and current reality of AI in breast cancer detection.[18]

Scientists would like to see further efforts improving the diagnostic accuracy in breast imaging, considering not only monetary costs but primarily the substantial psychological burden for women receiving false-positive findings even years after cancer has been ruled out. Interpreting the different patterns in mammography is challenging and requires a high level of specialization, routine, and experience. Mammograms of breast, being single-slice projection images, represent an ideal target of Artificial Intelligence technology. Deep-learning can be used to train artificial neural networks (ANNs) to acquire such diagnostic experience by scanning large number of mammograms. Highly specialized deep learning models show promising first results in the evaluation of diagnostic images for breast cancer.[19]

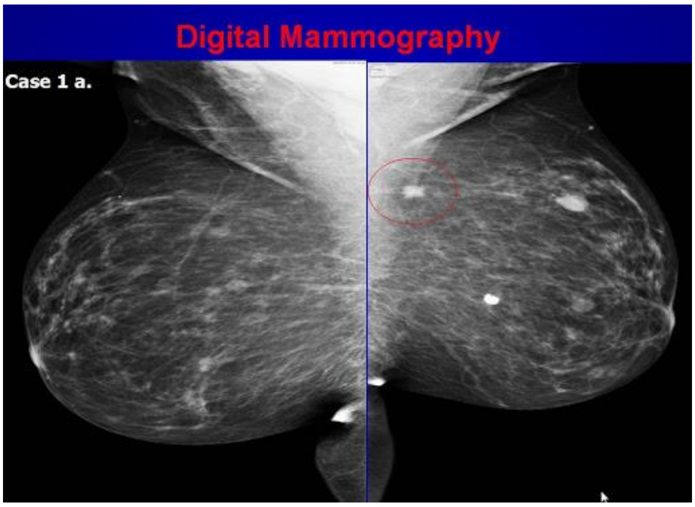

Figure 3. A digital mammogram is a radiographic examination showing the morphology of the anatomical elements of the breast tissue and any pathological lesions it may present. Today, three decades after the initial implementation of mammography continues to be the method of choice.

A recent study (2019) study aimed to develop an image-based deep learning (DL) model to predict the 5-year risk of breast cancer on the basis of a single breast mammograms radiographic (MR) examinations images from a screening examination. The study collected 1,656 consecutive breast MR images from screening examinations performed (2011-2013), to predict the risk of cancer developing within 5 years of the screening. The research team developed a logistic regression model based on traditional risk factors (the risk factor logistic regression [RF-LR] model) and a deep-learning model based on the MR image alone (the Image-DL model). The results showed that DL model can assess the 5-year cancer risk on the basis of a breast MR image alone, and it showed improved individual risk discrimination when compared with a state-of-the-art risk assessment model. These results offer promising preliminary risk assessment results.[20]

An artificial intelligence (AI) system for breast cancer screening outperformed radiologists in a recent study in *Nature*. The technique spotted more cancers and raised fewer false alarms. Researchers at Google Health and collaborators developed a deep-learning AI model for identifying breast cancer using screening mammograms from 2 large UK and US data sets. The test sets, which were not used to train or tune the system, included scans from 25, 856 women at 2 screening centers in England and 3,097 women at a US academic medical center. The researchers evaluated the AI system's cancer predictions and clinical radiologists' original decisions based on biopsy-confirmed breast cancer outcomes. In the US data set, the system produced 5.7% fewer false-positives and 9.4% fewer false-negatives than radiologists. The system also performed better on average than 6 US board-certified radiologists in a separate comparison involving 500 randomly selected mammograms from the US test set. Notably, most of the cancers identified only by the AI system were invasive. Two or more readers—the counterpart of US radiologists—interpret breast mammograms in the UK. In the UK data set, the AI system outperformed the first reader for specificity, resulting in fewer false-positives. It was noninferior for sensitivity but showed a tendency toward fewer false-negatives. The system performed on par with the second reader and with consensus judgments.[21]

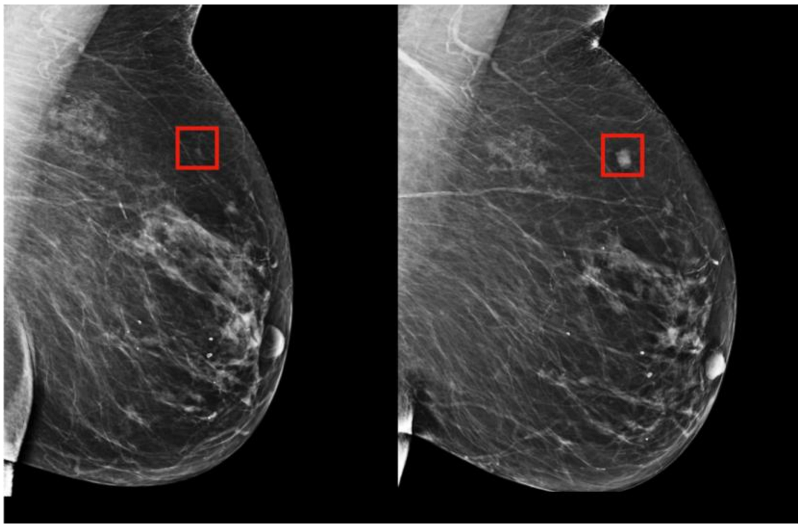

Figure 4. Using AI to predict breast cancer and personalize care image-based on deep learning model can predict breast cancer up to five years in advance. A team from MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL) and Massachusetts General Hospital (MGH) has created a new deep learning model that can predict from a breast mammogram if a patient is likely to develop breast cancer as much as five years in the future. Trained on mammograms and known outcomes from over 60,000 MGH patients, the model learned the subtle patterns in breast tissue that are precursors to malignant tumours.
Yala AS, Lehman C. Schuster T, Portnoi T. Barzilay R. A Deep learning mammography-based model for improved breast cancer risk prediction. *Radiology* 292(1):60-66, 7.5.2019. https://doi.org/10.1148/radiol.2019182716.

At present there is great excitement for applications of artificial intelligence (AI) in the health system and its promise of automating time-consuming and repetitive tasks in medicine, like reading breast mammograms and other digital screening pictures. But AI technologies also can help in the analysis of other type of medical visual input data. A recent example is AI models using AI algorithms in identifying diabetic retinopathy on fundus screening images better than specialized ophthalmologists. But screening breast mammographs (BM) for cancer is taking center stage because of huge numbers of BM produced every year in developed countries.[22]

A recent retrospective study (2020) examined large number of mammograms with AI algorithm. The validation involved 170,230 mammography examinations collected from five institutions in South Korea, the USA, and the UK, including 36,468 cancer positive confirmed by biopsy, 59,544 benign confirmed by biopsy (8,827 mammograms) or follow-up imaging (50,717 mammograms), and 74,218 normal. In the study 14 radiologists participated as readers and assessed each mammogram in terms of likelihood of malignancy (LOM), location of malignancy, and necessity to recall the patient, first without and then with assistance of the AI algorithm. The AI standalone performance was around 0·959-0968, significantly higher than that of the radiologists without AI assistance 0·810. With the assistance of AI, radiologists' performance was improved to 0·881. Researchers concluded that AI algorithm developed with large-scale mammography data showed better diagnostic performance in breast cancer detection compared with radiologists and radiologist improve their diagnosis with the help of AI.[23]

Early lung cancer diagnosis by artificial intelligence

Lung cancer remains the leading worldwide cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing close 18% of global cancer deaths. Also, lung cancer is the leading cancer in the USA with an estimated 160,000 deaths in 2018. Lung cancer screening using low-dose computed tomography (CT) scans has been shown from various studies that has the potential to reduce mortality by 20–43% if detected at the early stages. But interpreting correctly the lung computer tomography scans involved great challenges including inter-grader variability and high false-positive and false-negative rates.

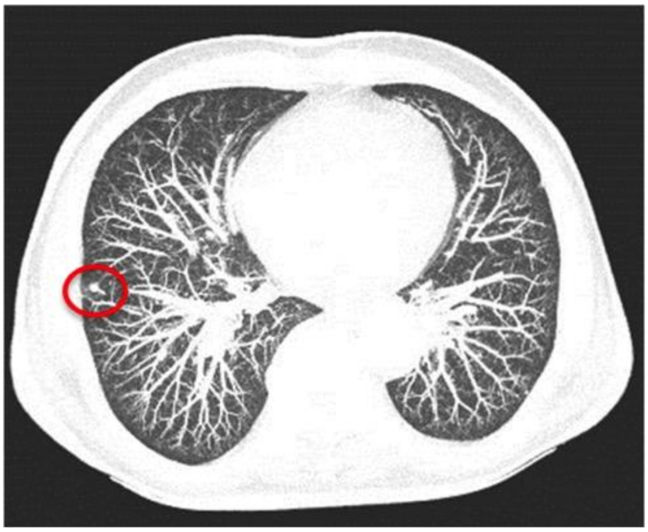

Figure 5. Illustrative computer tomography scan (CT) lung images showing lung nodules. These images have been post-processed using software applications. CT scans for lung cancer patient can detect small lung nodules that doctors can't see on standard x-rays. Recognizing these abnormalities in the lungs while they are still small allows doctors to detect lung cancer in its earliest stages when it can be more effectively treated and cured. Low dose CT screening to patients at a high risk for lung cancer will reduce death from the most deadly cancer worldwide, [https://www.ge.com/reports/post/129178111765/catching-cancer-with-low-dose-ct-helps-drop-lung-2/].

The USA (330 million population) with over 160,000 deaths every year from lung cancer has initiated the National Lung Cancer Screening Trial programme (National Cancer Institute) with the hope to reduce mortality by 20-43% from this type of deadly cancer, but inevitably the system produce a high number of CT scans and inevitable high percentage of false positives and false negatives. A group of scientists proposed to use a deep learning algorithm that used a patient's current and prior computed tomography (CT) volumes to predict the risk of lung cancer. Their model achieved a state-of-the-art performance (94.4% area under the curve) on 6,716 National Lung Cancer Screening Trial cases, and performed similarly on an independent clinical validation set of 1,139 cases. Researchers conducted two reader studies. When prior computed tomography imaging was not available, their model outperformed all six radiologists with absolute reductions of 11% in false positives and 5% in false negatives. Where prior computed tomography imaging was available, the model performance was on-par with the same radiologists. This creates an opportunity to optimize the screening process via computer assistance and automation. This study showed the potential for deep learning models to increase the accuracy, consistency and adoption of lung cancer screening worldwide.[24]

Researchers at Google are also trying to improve lung cancer screening. Medical groups in the U.S. and Canada already recommend screening certain people who are at high risk of lung cancer using computed tomography (CT) scans based on low-dose X-rays, and the same screening protocol is under consideration in the European Union. Computer scientists at Google wanted to see whether they could predict which people would go on to develop lung cancer by using AI to analyse low-dose CT scans of the lungs. They collected about 43,000 scans from almost 15,000 people that had been amassed by the National Lung Screening Trial (NLST), a study run by the US National Cancer Institute (NCI). Of those, 638 people did not have cancer at the time of the initial scan, but were diagnosed within one year, with the cancer confirmed by biopsy. The main goal was to try and predict whether someone ends up with lung cancer a year from when they got screened, or two years in some cases. [Kend J. Health IT Analytics, 26.5. 2019. https://healthitanalytics.com/news/google-develops-deep-learning-tool-to-enhance-lung-cancer-detection].

Another group of researchers developed a deep learning algorithm (DeepLR) using data from participants who had received at least two CT screening scans up to 2 years apart in the National Lung Screening Trial (NLST; training cohort). Double-blinded validation was done using data from participants in the Pan-Canadian Early Detection of Lung Cancer (PanCan) study (validation cohort). The primary analysis was to compare accuracy of DeepLR scores to predict lung cancer incidence at 1 year, 2 years, and 3 years with the Lung CT Screening Reporting & Data System (Lung-RADS) and volume doubling time, using time-dependent area under the receiver operating characteristic curve (AUC) analysis. The training cohort consisted of

25 097 participants from NLST and the validation cohort comprised 2294 individuals from PanCan. In the validation cohort, DeepLR showed good discrimination, with 1-year, 2-year, and 3-year time-dependent AUC values for cancer diagnosis of 0·968. The conclusion of this study showed that Deep Learning algorithm recognized patterns in both temporal and spatial changes and synergy among changes in nodule and non-nodule features.[25]

Another group of scientists used AI to examine non-small cell lung carcinoma and small cell carcinoma biopsies for early detection and correct diagnosis of lung cancer. The study aimed to assess which deep learning models perform best in lung cancer diagnosis. They used Non-small cell lung carcinoma and small cell lung carcinoma biopsy specimens which were stained. The specimen slides were diagnosed by two experienced pathologists (over 20 years). Also, several deep learning models were trained to discriminate cancer and non-cancer biopsies. The results of the study showed that deep learning models give reasonable AUC (area under the curve accuracy) from 0.8810 to 0.9119. Scientists concluded that deep learning analysis could help to speed up the detection process for lung carcinoma biopsies and keep the comparable detection rate with human expert observer.[26]

Artificial intelligence and thyroid cancer diagnosis

Thyroid ultrasound in clinical practice is the main examination that is used for both detection and characterization of thyroid lesions. The test is readily available, non-radiating and inexpensive. The main limitation on thyroid ultrasound is the interpretation of the ultrasound image by inexperienced radiologists. There is a risk of misdiagnosing a thyroid cancer and increasing the number of fine-needle aspiration biopsies. A study in 2017 described a new commercially available, computer-aided diagnosis (CAD) system using artificial intelligence (AI) for thyroid ultrasound identification of malignant thyroid nodules, and its performance in evaluating the diagnosis of malignant and categorization of nodule characteristics. The study used 102 thyroid nodules from 89 patients. An experienced radiologist reviewed the ultrasound image characteristics of the thyroid nodules, while another radiologist assessed the same thyroid nodules using the CAD system, providing ultrasound characteristics and a diagnosis of whether nodules were benign or malignant. The two diagnostic methods were compared. The CAD system showed a similar sensitivity as the experienced radiologist (90.7% vs. 88.4%, $p > 0.99$), but a lower specificity and a lower area under the receiver operating characteristic. The conclusion of the scientists was that the sensitivity of the CAD system using AI for malignant thyroid nodules was as good as that of the experienced radiologist, while specificity and accuracy were lower than those of the experienced radiologist. The CAD system showed an acceptable agreement with the experienced radiologist for characterization of thyroid nodules.[27]

A recent study (2019) in China used deep convolutional neural network (DCNN) models to improve the diagnostic accuracy of thyroid cancer by analysing sonographic imaging data from clinical ultrasounds. This was a retrospective, multicohort, diagnostic study using ultrasound images sets from three hospitals in China. Scientists developed and trained the DCNN model on the training set, 131,731 ultrasound images from 17,627 patients with thyroid cancer and 180,668 images from 25,325 controls from the thyroid imaging database at Tianjin Cancer Hospital. The DCNN model achieved high performance in identifying thyroid cancer patients in the validation sets tested, with area under the curve values of 0·948-0.912. The DCNN model also showed improved performance in identifying thyroid cancer patients versus analysis data and malignancy prognosis from skilled radiologists.[28]

Early detection of gastric cancer by artificial intelligence

It is widely accepted among specialists that oesophageal cancer and gastric cancer are potentially curable if detected at early stages, yet most patients have advanced stages at diagnosis due to non-specific symptoms and late clinical presentation. Artificial intelligence (AI) models in clinical medicine and especially in gastrointestinal (GI) endoscopy have the potential to improve the quality of GI endoscopy at all levels. The new methods will is hoped to compensate for humans' errors and bring more diagnostic accuracy, making endoscopic procedures more efficient and of higher quality.[29]

Diagnostic systems of image recognition using AI with deep learning through convolutional neural networks (CNNs) has dramatically improved in medical fields. Scientists (Dpt of Gastroenterology, Cancer Institute Hospital Ariake, Tokyo, Japan), used a CNN-base on Single Shot MultiBox Detector architecture and trained using 13,584 endoscopic images of gastric cancer. To evaluate the diagnostic accuracy, an independent test set of 2,296 stomach images collected from 69 consecutive patients with 77 gastric cancer lesions was applied to the constructed CNN. The CNN required 47 seconds to analyze 2,296 test images and correctly diagnosed 71 of 77 gastric cancer lesions with an overall sensitivity of 92.2%, and 161 non-cancerous lesions were detected as gastric cancer, resulting in a positive predictive value of 30.6%. Seventy of the 71 lesions (98.6%) with a diameter of 6 mm or more as well as all invasive cancers were correctly detected. The research team concluded that the CNN system for detecting gastric cancer could process numerous stored endoscopic images in a very short time with a clinically relevant diagnostic ability. It may be well applicable to daily clinical practice to reduce the burden of medical endoscopists.[30]

In China researchers used AI platforms and deep learning algorithms in medical imaging. They aimed to develop and validate the Gastrointestinal Artificial Intelligence Diagnostic System (GRAIDS) for the diagnosis of upper gastrointestinal cancers through analysis of imaging data from clinical endoscopies. The research group used a multicentre, case-control, diagnostic study from six hospitals of different tiers (ie, municipal, provincial, and national) in China. The images of consecutive participants were retrieved from all participating hospitals and all patients with upper gastrointestinal cancer lesions (including oesophageal cancer and gastric cancer) that were histologically proven malignancies were eligible for this study. The study used 1,036, 496 endoscopy images from 84,424 individuals that were tested by the system GRAIDS. The diagnostic accuracy in identifying upper gastrointestinal cancers was 0·955 in the internal validation set, 0·927 in the prospective set, and ranged from 0·915 to 0·977 in the five external validation sets. GRAIDS achieved diagnostic sensitivity similar to that of the expert endoscopist. Scientists concluded that GRAIDS achieved high diagnostic accuracy in detecting upper gastrointestinal cancers, with sensitivity similar to that of expert endoscopists and was superior to that of non-expert endoscopists and can be useful to community-based hospitals in improving their effectiveness in upper gastrointestinal cancer diagnoses.[31]

Artificial intelligence in early diagnosis of oral cancer

Squamous cell carcinoma of the oral cavity is the 6th most common malignancy in the world. The WHO estimates an incidence of 529,000 new cases of oral cancer each year, causing more than 300,000 deaths. Early diagnosis is the most important determinant of oral and oropharyngeal squamous cell carcinoma (OPSCC) outcomes, yet most of these cancers are detected late, when outcomes are poor. Typically, nonspecialists such as dentists screen for oral cancer risk, and then they refer high-risk patients to specialists for biopsy-based diagnosis. The clinical appearance of oral mucosal lesions is not an adequate indicator of their diagnosis, or risk level with poor sensitivity and specificity. Overall, 60% of all people with oral cancer will survive for 5 years or more. The earlier the stage at diagnosis, the higher the chance of survival after treatment. This makes timely diagnosis all the more important. [Healthline, 2019, https://www.healthline.com/health/oral-cancer#stages].

A recent overview described the emerging optical imaging modalities and novel artificial intelligence-based approaches to evaluate their individual utility and implications for improving oral cancer detection and outcomes. The principles of image-based approaches to detecting oral cancer are placed within the context of clinical needs and parameters. Artificial intelligence approaches and specific algorithmic models are beginning to have considerable impact in improving diagnostic accuracy in some fields of early diagnosis of cancer, in particular to oral cancer. The overview described these studies which demonstrated that artificial intelligence approaches combined with imaging can have considerable impact on oral cancer outcomes, with applications ranging from low-cost screening with smartphone-based probes to algorithm-guided detection of oral lesion heterogeneity and margins using optical coherence tomography.[32]

Another recent study (2019) developed a deep learning algorithm for automated, computer-aided oral cancer detecting system by investigating patient hyperspectral images. The study proposed regression-based partitioned deep learning algorithm, to compare the performance with other techniques by its classification accuracy, specificity, and sensitivity. For the accurate medical image classification objective, researchers demonstrated a new structure of partitioned deep Convolution Neural Network (CNN) with two partitioned layers for labeling and classify by labeling region of interest in multidimensional hyperspectral image. The performance of the partitioned deep CNN was verified by classification accuracy. The results showed classification accuracy of 91.4% with sensitivity 0.94 and a specificity of 0.91 for 100 image data sets training for task classification of cancerous tumour with benign and for task classification of cancerous tumor with normal tissue accuracy of 94.5% for 500 training patterns. Researchers compared the obtained results from another traditional medical image classification algorithm. From the obtained result, scientists concluded that the quality of diagnosis is increased by proposed regression-based partitioned CNN learning algorithm for a complex medical image of oral cancer diagnosis.[33]

Artificial Intelligence and skin cancer diagnosis

Skin cancer is the most common malignancy in fair-skinned populations, and melanoma accounts for the majority of skin cancer–related deaths worldwide. Despite special training and the use of dermoscopes, dermatologists only rarely achieve clinical test sensitivities greater than 80%. In 2017, Esteva *et al.* were the first to report a deep-learning convolutional neural network (CNN) image classifier that performed as well as 21 board-certified dermatologists when identifying images with malignant lesions. The CNN deconstructed digital images of skin lesions and generated its own diagnostic criteria for melanoma detection during training. Several follow-up publications by other authors have demonstrated dermatologist-level skin cancer classification by using deep neural networks (CNN), But these publications involved limited numbers of dermatologists and proprietary image databases.[34,35,36]

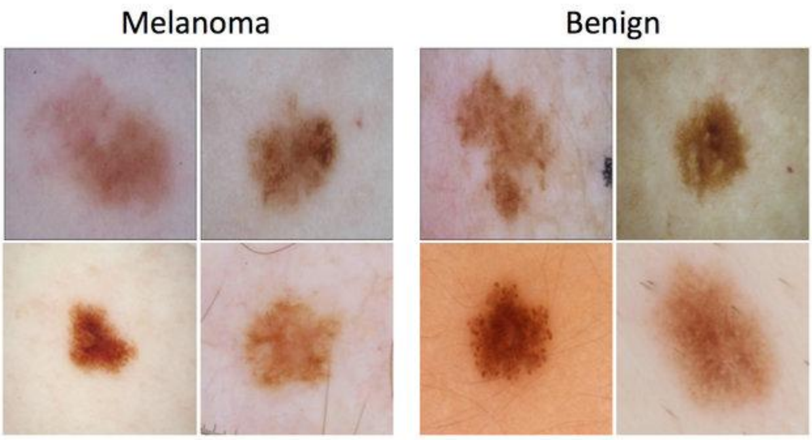

Figure 6. Dermoscopy, the microscopic examination of the skin surface, has been used to evaluate skin lesions and detection of melanoma. Its value, however, has been questioned for melanoma-in-situ (MIS). Examples of lesion classification task. Left example dermoscopic images of melanoma. Right example of dermoscopic images of benign nevi. [from, Gutman DA, Codella N, Celebi ME, et al. Skin Lesion Analysis toward Melanoma Detection: A Challenge at the International Symposium on Biomedical Imaging (ISBI) 2016, hosted by the *International Skin Imaging Collaboration* (ISIC), May 2016.

In a recent study (2019) researchers trained a CNN with enhanced techniques to classify images of suspect lesions as melanoma or atypical nevi by the use of open-source images exclusively. The classification results of the CNN were compared with the efforts of 157 dermatologists from 12 German university hospitals of all levels of training. They used methods from enhanced deep learning to train a convolutional neural network with 12,378 open-source dermoscopic images. Also, they used 100 images to compare the performance of the CNN to that of the 157 dermatologists. Outperformance of dermatologists by the deep neural network was measured in terms of sensitivity, specificity and receiver operating characteristics. The results showed that the mean sensitivity and specificity achieved by the dermatologists with dermoscopic images was 74% and 60%, respectively. At a mean sensitivity of 74%, the CNN exhibited a mean specificity of 86.5%. At a mean specificity of 60%, a mean sensitivity of 87.5% was achieved by the algorithm used. So, the conclusion was that a CNN trained by open-source images exclusively outperformed 136 of the 157 dermatologists and all the different levels of experience (from junior to chief physicians) in terms of average specificity and sensitivity.[37]

AI for interpretation of colorectal and hepatocellular (liver) cancer

Hepatocellular (liver) carcinoma is the most common type of primary liver cancer and occurs mostly in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection. Also, it is more common in people who drink excessive alcohol and who have an accumulation of fat in the liver. Tests (blood, liver biopsy) and imaging (CT or MRI) can be used for early diagnosis of hepatocellular carcinoma.

A recent review study (2019) investigated the use of AI models, such as convolutional neural networks (CNNs) that have been used in the interpretation of images and the diagnosis of hepatocellular cancer (HCC) and liver masses. CNN, a machine-learning algorithm similar to deep learning, has demonstrated its capability to recognise specific features that can detect pathological lesions. Researchers used data from various databases and collected studies which analysed pathological anatomy, cellular, and radiological images of hepatocellular cancer or liver masses. With the help of CNNs medical experts identified malignant lesions, differentiating cancerous ones from other types of lesions. A total of 11 studies that met the selection criteria and were consistent with the aims of the study were identified. The studies demonstrated the ability to differentiate liver masses or differentiate HCC from other lesions (6 studies), HCC from cirrhosis or development of new tumours (*3 studies*), and HCC nuclei grading or segmentation (*2 studies*). The CNNs showed satisfactory levels of accuracy. The researchers concluded that overall there was an optimal level of accuracy of the CNNs used in segmentation and classification of liver cancers images.[38]

Colorectal cancer forms when the DNA in cells in the colon or rectum develop mutations. The colorectal cancer has certain risk factors that are strongly linked to the disease, including diet, tobacco smoking and heavy alcohol use. Also, people with certain hereditary cancer syndromes are at higher risk. Diets that are high in red and processed meats may increase colorectal cancer risks. Frying, grilling, broiling or other methods of cooking also contribute to an increased risk. A diet rich in fruits, vegetables and high-fiber grains may help reduce risk of developing colorectal cancer. The diagnosis of colorectal at an early stage is crucial to enhance the success of treatment approaches.

A recent study (2020) developed a biomarker of patient outcome after primary colorectal cancer resection by directly analysing scanned conventional haematoxylin and eosin stained sections using deep learning. The study used 12,000,000 image tiles from patients with a distinctly good or poor disease outcome from 4 cohorts to train a total of 10 convolutional neural networks (CNNs), purpose-built for classifying supersized heterogeneous images. A prognostic biomarker integrating the 10 networks was determined using patients with a non-distinct outcome. The marker was tested on 920 patients with slides prepared in the UK, and then independently validated according to a predefined protocol in 1,122 patients treated with single-agent capecitabine using slides prepared in Norway. The study found that 828 patients from 4 cohorts had a distinct outcome and were used as a training cohort to obtain clear ground truth. 1,645 patients had a non-distinct outcome and were used for tuning. The biomarker provided a hazard ratio for poor versus good prognosis of 3·84 in the primary analysis of the validation cohort, and 3·04 after adjusting for established prognostic markers significant in univariable analyses of the same cohort.[39]

Scientists in China developed AI models for the accurate and robust pathological image analysis for colorectal cancer (CRC) diagnosis. They used state-of-the-art transfer-learned deep convolutional neural network (CNNs) in artificial intelligence (AI), as a novel patch aggregation strategy for clinic CRC prediction/diagnosis using weakly labeled pathological whole slide image (WSIs) patches. This approach was trained and validated using an unprecedented and enormously large number of 170,099 patches, >14,680 WSIs, from >9,631 subjects that covered diverse and representative clinical cases from multi-independent-sources across China, U.S., and Germany. Researchers analyse the tests and found the innovative AI system was consistently nearly perfectly agreed with (average Kappa-statistic 0.896) and even often better than most of the experienced expert pathologists when tested in diagnosing CRC WSIs from multi-centers. The average area curve (AUC) of AI was greater than that of the pathologists (0.981 vs 0.970). Researchers concluded that the AI system can handle large amounts of WSIs consistently and robustly without potential bias due to fatigue commonly experienced by clinical pathologists. Hence, it will drastically alleviate the heavy clinical burden of daily pathology diagnosis, and improve the treatment for CRC patients.[40]

Conclusions

Screening programmes for early cancer identification and accurate diagnosis started many decades ago in most developed countries. Scientific breakthroughs and technological advances in areas such as genetics, and medical imaging promoted the accurate prognosis of most cancers at an earlier stage. The result was that most cancers now can be cured and survival rates of cancer patients has been improved. However, accuracy in medical imaging diagnosis is not 100%, with cancer professionals seeing up to 20% percent false negatives in chest X-rays and mammograms. False positive diagnosis of cancer is also common causing great anxiety to patients and healthy people. For example, the sensitivity of breast mammography is about 87 percent. One of the biggest challenges of the diagnostic methods is early detection, which is more difficult since the malignant growth is extremely small and difficult to detect. According to numerous studies if a cancer patient is diagnosed early, the chance of survival increases exponentially. It is known that more than 80% of breast, ovarian, prostate, lung cancer deaths are preventable to a high degree if detected early. The diagnostic tools at the disposal of specialists despite their vast improvements caused long hours of evaluation and massive managerial work for the hospital staff. False positive and false negative medical assessments caused substantial problems for the reputation of health systems. Most physicians spent much more time performing data entry and desk work during the office consultation than actually talking to patients

But new developments came to the rescue in the last 10 years with Artificial Intelligence (AI) systems that poised to revolutionize and transform medical scanning practice with various automated technologies in the diagnosis, treatment and prediction of outcomes among cancer patients. Dramatic developments occurred in recent years for early diagnosis by AI helping to improve accuracy, much earlier diagnosis of cancer and reduction in false identifications. AI can help in the collection of patients' data, physical examinations, and laboratory tests. Also, AI can examine and interpret collected data and medical results, provide diagnosis based on collected health related information and matching it with previous information and knowledge, Finally, AI can select appropriate treatment plans from the diagnosis and administer to patients, while re-evaluating the diagnosis and treatments. In this respect AI may do better than doctors in many ways, but increased use of AI could raise certain ethical dilemmas and bring about many issues of concern. The vast majority of AI applications in cancer detection at an early stage were beneficial to the medical community and with overall improvements in machine learning and new algorithms their accuracy improved substantially. Researchers and specialists working in the field of evaluating cancer scanning images admit that AI methodologies help reduce diagnosis time, costs, and patients' anxiety as well as producing accurate image-recognition tasks for most cancer types. Medical fields that rely on imaging data, including radiology, pathology and cancer diagnosis, have already begun to benefit from the implementation of AI methods. AI excels at recognizing complex patterns in imaging data and can provide a quantitative assessment in an automated fashion. More accurate and reproducible radiology assessments can then be made when AI is integrated into the clinical workflow as a tool to assist physicians and the health system.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. *Global and Regional Estimates of the Incidence and Mortality for 38 Cancers*: GLOBOCAN 2018. Lyon: International Agency for Research on Cancer/World Health Organization; 2018
2. Bray F, Ferlay J, Isabelle Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 68:394-424, 2018.
3. Hawkes N. Cancer survival data emphasise importance of early diagnosis. *Brit Med J* 364:1408-1411, 2019.
4. Cancer Research UK. Why is early diagnosis important**?** Finding and treating cancer at an early stage can save lives. [https://www.cancerresearchuk.org/about-cancer/cancer-symptoms/why-is-early-diagnosis-important]
5. Thun MJ, Henley SJ, Travis WD. Lung cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. *Cancer Epidemiology and Prevention.* 4th ed. New York, NY: Oxford University Press, pp,:519-542, 2018.
6. Jha P. Avoidable global cancer deaths and total deaths from smoking. *Nat Rev Cancer*. 9:655-664, 2009.
7. Siegel MPH, Miller KD, Ahmedin Jemal DVM. Cancer statistics, 2020. *CA: A Cancer J Clinicians* 8.1.2020, https://doi.org/10.3322/caac.21590.
8. Emmons KM, Colditz GA. Realizing the potential of cancer prevention: the role of implementation science. *N Engl J Med* 376:986–990, 2017.
9. Rebbeck TR, Burns-White K, Chan AT, et al. Precision prevention and early detection of cancer: Fundamental principles. *Cancer Discovery* 8(7):803-811, 2018.
10. American Cancer Society. *Cancer Prevention and Early Detection . Facts and* Figures 2019-2020, Atlanta, ACS, 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-prevention-and-early-detection-facts-and-figures/cancer-prevention-and-early-detection-facts-and-figures-2019-2020.pdf].
11. American Cancer Society, 2019 [https://www.cancer.org/healthy/find-cancer-early/tests-to-find-and-diagnose-cancer.html].
12. United Nations, WHO, Sustainable Development. Early cancer diagnosis, better trained medics can save lives, 2019. https://www.un.org/ sustainabledevelopment/blog/2017/02/who-early-cancer-diagnosis-better-trained-medics-can-save-lives-money/].
13. Cancer Research UK. Why is early diagnosis important for survival of cancer patients, 2019, https://www.cancerresearchuk.org/about-cancer/cancer-symptoms/why-is-early-diagnosis-important].
14. Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. *Minimally Invasive Therapy Allied Technologies* 28(2):73-81, 2029. Published online: 27 Feb 2019
15. Becker A. Artificial intelligence in medicine: What is it doing for us today? Literature Review. *Health Policy &Technology* 8(2):198-205, 2019.

16. Chen L-K. Artificial intelligence in medicine and healthcare. *J Clin Gerontology & Geriatrics* 9(3):77-78, 2018.
17. Scerri M, Grech V. Artificial intelligence in medicine. *Early Human & Development* 20/3/2020, 105017, on line.
18. McKinney SM, Sieniek M, Shetty S, et al. International evaluation of an Artificial Intelligence (AI) system for breast cancer screening. *Nature* 577:89-94, 2020.
19. Becker A S, Marcon, M; Ghafoor S, et al. Diagnostic accuracy of a multipurpose image analysis software in the detection of breast cancer. *Investigative Radiology* 52 (7): 434-440, 2017.
20. Tally Portnoi, Adam Yala, Tal Schuster, Regina Barzilay, et al. Deep learning model to assess cancer risk on the basis of a breast MR image alone. *Am J Roentgenology* 213:227-233, 2019.
21. Abbasi J. Artificial Intelligence improves breast cancer screening in study. *JAMA* 323(6):499, 2020. doi:10.1001/jama.2020.0370.
22. Lee CI, Elmore JG. Artificial intelligence for breast cancer imaging: the new frontier? *J Natl Cancer Inst* 111(9):875-876, 2019. doi:10.1093/jnci/djy223.
23. Kim Y-E, Kim HH, Han B-K, et al. Changes in cancer detection and false-positive recall in mammography using artificial intelligence: a prospective, multireader study. *The Lancet Digital Health* 2(3):E138-E148, 2020.
24. Ardila D, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, et al. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nature Medicine* 25 (6) :954-961, 2019.
25. Huang P, Lin CT, Li Y, et al. Prediction of lung cancer risk at follow-up screening with low-dose CT: a training and validation study of a deep learning method. *The Lancer Digital Health* 1(7):P353-362, 2019.
26. Li Z, Hu Z, Xu J, Tan T, et al. Computer-aided diagnosis of lung carcinoma using deep learning - a pilot study. *Computer Vision & Pattern Recognition*. arXiv:1803.05471, 2018.
27. Choi YJ, Bae JH, Park HS, et al. A Computer-aided diagnosis system using artificial intelligence for the diagnosis and characterization of thyroid nodules on ultrasound: initial clinical assessment. *Thyroid* 27(4):546-552, 2017.
28. Li X, Zhang SD, Zhang Q, et al. Diagnosis of thyroid cancer using deep convolutional neural network models applied to sonographic images: a retrospective, multicohort, diagnostic study. *The Lancet Oncology* 20(2): 193-201, 2019.
29. Hajjar AE, Rey J-F. Artificial intelligence in gastrointestinal endoscopy: general overview. *Chinese Medical J* (Engl) 133(3): L326-334, 2020.
30. Hirasawa T, Aoyama K, Tanimoto T, et al. Application of artificial intelligence using a convolutional neural network for detecting gastric cancer in endoscopic images. *Gastric Cancer* 21:653-669, 2018.
31. Luo H, Xu G, Li C, et al. Real-time artificial intelligence for detection of upper gastrointestinal cancer by endoscopy: a multicentre, case-control, diagnostic study. *Lancet Oncology* 20(12):164501654, 2019.

32. Ilhan B, Lin K, Guneri P, Wilder-Smith P. Improving oral cancer outcomes with imaging and artificial intelligence. *J Dent Res* 99(3):241-248, 2020.
33. Jeyarai PR, Nadar ERS. Computer-assisted medical image classification *for* early diagnosis of oral cancer employing deep learning algorithm. *J Cancer Res Clinical Oncology* 145:829-873, 2019.
34. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 542:115-116, 2017.
35. Haenssle H, Fink C, Schneuderbauer R, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermtologists. Ann Oncol 28:1836-1842, 2018.
36. Brinker TJ, Hekler A, Utikal JS, et al. Skin cancer classification using convolutional neural networks: systematic review. *J Med Internet Res* 20:e11936, 2018.
37. Brinker TJ, Hekler A, Enk AH, et al. Deep learning outperformed 136 of 157 dermatologists in a head-to-head dermoscopic melanoma image classification task. *European J Cancer* 113:47-54, 2019.
38. Azer SA. Deep learning with convolutional neural networks for identification of liver masses and hepatocellular carcinoma: A systematic review. *World J Gastrointest Oncol* 11(12):1218-1230, 2019.
39. Skrede OJ, De Raedt S, Kleppe A, Hveem TS, et al. Deep learning for prediction of colorectal cancer outcome: a discovery and validation study. *Lancet* 395:350-360, 2020.
40. Wang K-S, Yu G, Xu C, et al. Accurate diagnosis of colorectal cancer based on histopathology images using Artificial Intelligence. *BioRxin The Preprint Server of Biology*, 17 March 2020, [doi: https://doi.org/10.1101/2020.03.15.992917].