

REVIEW

Cancer prevention: state of the art and future prospects

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Summary

Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs that specifically target tumor cells is leading to increasingly expensive treatments, which may be affordable only for few patients. Prevention, and particularly primary prevention, is an effective way of addressing the challenging issue of cancer, since between a third and a half of cancers could be prevented on the basis of our current knowledge of risk factors. Moreover, prevention is cost-effective, its effects are not limited to high-risk subjects but extend to the entire population, and it is not dependent on socio-economic status. Regulatory measures can have a broad impact, even on future generations; by empowering and educating subjects, promoting healthy behaviours and teaching self-care, they can trigger a virtuous cycle. In recent decades, oncology has shifted from being merely reactive to being proactive; this shift has led to the development of so-called “P4 medicine”, where the 4 Ps stand for “preventive”, “predictive”, “personalized” and “participatory”. Prevention programs are an important part of the effort to control cancer, as they are able to reduce both the

incidence of cancer and mortality. For instance, screening for colorectal, breast and cervical cancer is reducing the burden of these common tumors. Anti-cancer vaccines, both prophylactic and therapeutic, constitute another important preventive tool. Although progress has been made in these areas, much remains to be done. With regard to screening programs, coverage could be increased by introducing new, more acceptable, less invasive tests, stratifying screening through correlation with anamnestic, clinical, radiological and genomic data (so-called “population-based personalized cancer screening”), and exploiting new information and communication technologies, such as smartphone applications or personalized text messages (so-called “screening 2.0”). Advocacy and recommendations by physicians can also play a role, in that eligible subjects need to be able to discuss their doubts and their perceived psycho-social barriers. However, new screening initiatives should be implemented only after a careful health technology assessment has been performed within the framework of evidence-based medicine, organized screening programs have been strengthened and opportunistic or spontaneous programs have been limited.

The global burden of cancer

Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs [1, 2]. Despite striking advances in the field of molecular oncology, combating cancer remains a challenge. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs that specifically target tumor cells (so-called individualized drug therapy) is driving up the costs of treatment [2, 3]. As a consequence, the benefit of these achievements may be scarcely affordable and the costs could dramatically impact on health-care systems [2, 3]. Despite its alleged advantages, the implementation of genomics in routine clinical practice remains far from cost-effective [3].

As Vineis and Wild maintain [1], prevention, and specifically primary prevention, is a particularly effective way to address the challenging issue of cancer.

Primary and secondary prevention offers several advantages:

1. As such programs are population-based, they could benefit people other than those directly targeted [1].

2. As cancer has a long latency period, its causes and risk factors could be eliminated or reduced in the long term, thus yielding a broader impact on Public Health. Interventions are not limited to surgical or pharmacological treatments, but include a variety of programs and measures aimed at correcting unhealthy lifestyles and favouring continuous transformation, for example through regulation against occupational or environmental exposure to certain substances. By empowering and educating people, promoting healthy behaviors and teaching self care, a virtuous cycle can be set in motion, meaning that these preventive efforts do not need to be renewed with every generation. This is important in periods of economic and financial hardship, when public resources are scarce [1]. Moreover, some regulatory measures could help to prevent various types of cancer and other pathologies; for example, cigarette smoking, besides being associated with lung cancer, could lead to an increased risk of developing breast cancer [4], prostate cancer [5], lymphoma [6] and other diseases [7]. In addition, avoiding exposure to

carcinogenic substances may contribute to preventing other non-communicable diseases (NCDs), such as cardiovascular, reproductive, endocrine and dys-metabolic pathologies [1]. In conclusion, a single public health measure would have multiple, enduring “cascade effects” which a single clinical intervention would not have.

- 3) Prevention is cost-effective and can impact positively on socio-economic inequalities [8-12]. Since up to half of cancers could be prevented on the basis of present knowledge of etiopathogenesis and risk factors [1], preventive medicine can act as a rapid and effective means of connecting research with clinical practice [13].

Primary and secondary prevention should therefore be regarded as a priority for global cancer control [1, 14].

Oncology in the framework of P4 medicine

In recent decades, oncology has shifted from being merely reactive and has adopted a proactive model within the framework of so-called “P4 medicine” [15, 16], where the 4 Ps stand for predictive, preventive, personalized and participatory. Advances in the field of molecular biology, high-throughput technologies (HTTs) and “omics” sciences, as well as in imaging techniques and mathematical and computational modelling, have led to the discovery of biomarkers which can be used to predict the onset, course and prognosis of tumors; this enables diagnosis, treatment and prevention to be correlated within a highly integrated, coherent framework. Rather than being “one-size-fits-all”, P4 medicine is individually tailored to the specific needs of the patient. Screening and prevention play a major role in an approach that is gradually shifting from disease to wellness.

It should be emphasized that this new effort requires a holistic view at all levels [17]; cancer is a complex adaptive system (CAS), the etiopathogenesis of which can be unravelled only by means of a systems approach (systems biology and “omics” sciences). Cancer management requires multi-level system-based management [18]. Organized screening is a highly standardized form of “systems screening”; as it is constantly monitored through quality check and process indicators and relies on evidence-based protocols and guidelines, it differs from opportunistic or spontaneous screening [19].

In the system of systems (SoSs) perspective, cancer screening programs can be integrated into health promotion plans, becoming “teachable moments”, during which people can be sensitized to the importance of proper nutrition, physical activity and other healthy behaviors [20]. In this way, as already mentioned, a virtuous cycle with cascade effects can be set in motion.

The following sections present an overview of the currently available organized cancer screening tests, a discussion of their present state and future prospects, and a brief look at the topic of anti-cancer vaccines.

PREVENTION OF CERVICAL CANCER

Cervical cancer is the tenth most frequent cancer and the third most common cancer in terms of mortality, after breast and colorectal cancer [21-23], though this trend is decreasing.

Risk factors for developing cervical cancer include: tobacco and alcohol consumption, a history of genital warts, early age on first sexual intercourse or first pregnancy, multiparity, sexual promiscuity and unprotected sex, a history of sexually transmitted diseases (STDs), low socio-economic status and low educational level, Human Immunodeficiency Virus (HIV) infection and other conditions resulting in immunosuppression [21-23].

Screening modalities include [21-23]: 1) cervical cytology (Papanicolaou or Pap smear), which may be conventional or liquid-based (LBC), and may be assisted by automated screening technologies (ASTs) [24]; 2) colposcopy, which involves direct visual inspection (DVI) performed by using 3-5% acetic acid (VIA), 3-5% acetic acid and magnification (VIAM), or Lugol’s iodine (VILI); and 3) HPV-DNA testing [25]. Other modalities, such as cervicoscopy, cervicography, colpohysteroscopy/microcolpohysteroscopy, speculscopy (a magnified chemiluminescent screening examination) and polar probes (such as spectrophotometry/microspectrophotometry, Raman scattering and fluorescence spectroscopy), are still experimental and can be used as second-line techniques for the further evaluation and assessment of abnormal results. A next-generation assay, which is quite promising, is HPV mRNA testing [26-28].

According to the 2010 European Guidelines for Quality Assurance of Cervical Cancer Screening [29], the American Cancer Society (ACS), the American College of Obstetricians and Gynaecologists (ACOG) and the Centers for Disease Control and Prevention-Advisory Committee on Immunization Practices (CDC-ACIP), the age at which screening should be started is in the range of 20-30 years, but preferably not before 25 years (in Italy, for example, the age is 25 years). Women aged 21-29 years should undergo a Pap smear every 3 years, regardless of their sexual activity. If the result of the test is abnormal (such as atypical cells of undetermined significance, or ASCUS), the woman should undergo HPV-DNA testing [29, 30]. Women over the age of 29 years can be screened every 5 years with a combination of HPV-DNA testing and Pap smear. The age at which screening should be discontinued is in the range of 60-65 years of age (in Italy, for example, it is 65 years), in the absence of abnormal results [29, 30].

Recently, four European randomized controlled trials (RCTs) (Swedescreen in Sweden, POBASCAM in the Netherlands, ARTISTIC in Great Britain and NTCC in Italy) have shown that HPV-based screening started at the age of 30 years, with screening intervals of up to 5 years, is still effective in protecting women against invasive carcinoma [31]. However, although this strategy appears to be the most cost-effective, it is applied in few countries [32].

Compliance with cervical cancer screening programs is still unsatisfactory and strongly age-dependent [33].

Variables which can predict adherence to screening include educational level, culture, psychosocial issues and marital status [33, 34].

High-quality cervical screening helps to reduce the incidence of cervical cancer and mortality. In Italy, the incidence of squamous cell and invasive cancers has significantly decreased from 11.6/100,000 to 8.7/100,000 since the introduction of cervical screening [35].

PREVENTION OF COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer in men, after lung and prostate cancer, and the second most frequent cancer in women after breast cancer, with more than 1,360,000 cases per year (10% of the total cancer burden). Its incidence increases with age, and more men than women are affected [36]. CRC is a major cause of cancer-related death, ranking fourth after lung, liver and stomach cancer [37].

Risk factors for developing CRC are: obesity [38], consumption of red and highly processed meat [39], tobacco and alcohol use, a history of inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease, a family history of inherited CRC, and syndromes such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) [40]. Vegetable consumption and physical activity are protective factors [41].

CRC can be screened in several ways [42, 43], the most commonly used method being the stool test, known as fecal occult blood test (FOBT). Variants of this test are the guaiac-based FOBT (gFOBT), the fecal immunochemical test (FIT) and the stool DNA test (sDNA).

In the event of positivity, flexible sigmoidoscopy (FS) or total colonoscopy (TC) can be performed [37]. Computed tomography (CT) scans (CT colonography, or CTC) can be used in those patients in whom TC is contraindicated or if it has not been possible to perform a complete TC [37].

Other tests, which are still experimental, are double-contrast barium enema (DCBE), colon capsule endoscopy (CCE) and high-resolution colonoscopy (HRC) [37]. The Epi proColon® 2.0 test (Epigenomics AG) is a highly sensitive and specific new-generation test; this assesses aberrant methylated patterns of the septin 9 gene, which is usually hypermethylated in CRC [44].

CRC screening should be started at the age of 50 years; subjects who are particularly at risk for CRC should be screened earlier and more frequently. According to the guidelines, screening options for eligible subjects include: FOBT every year; DCBE every 5 years; FS every 5 to 10 years, usually combined with FOBT every 1-3 years; virtual colonoscopy (VC) every 5 years; colonoscopy every 10 years. In the event of positivity, colonoscopy should be performed [37].

Adherence to the program is still low: for example, a recently published systematic review has found that in 2000, in the USA, only 34% of the population complied with CRC screening following the recommendations and guidelines [45]. It has been observed that doctors, particularly family doctors, play a major role in increas-

ing participation by discussing the benefits and usefulness of screening with their patients [46, 47].

High-quality CRC screening [48] has been seen to reduce the incidence of CRC by 33% and mortality due to CRC by 43% [36].

PREVENTION OF BREAST CANCER

Despite advances in treatment and diagnosis, breast cancer is still a serious Public Health concern [49], with 1,384,155 expected new cases worldwide and an estimated 459,000 deaths [49]. Moreover, both incidence and related mortality have increased by 18% since 2008. According to the ACS, breast cancer affects one in every eight women in the US. It is estimated that the annual global burden of breast cancer will reach 3.2 million new cases by 2050 [49].

Risk factors for developing a breast cancer include: breast size [50], lack of physical activity, overweight and obesity [51-53], infertility and nulliparity, first full-term pregnancy at the age of 30 years or later, early age on menarche, tobacco and alcohol use, hormone replacement therapy (HRT) such as oestrogen and progestin, exposure to diethylstilbestrol (DES), inherited genetic anomalies (BRCA1, BRCA2) [49, 53, 54], and Cowden and Li-Fraumeni syndrome [53, 54]. Breastfeeding and vegetable consumption are protective factors.

Mammography is the gold standard in early breast cancer detection; screening results are communicated by means of the highly standardized "breast imaging reporting and database system" (BI-RADS).

In 2009-2010, the US Preventive Services Task Force (USPSTF) issued new updated recommendations for routine mammography screening, after examining and comparatively assessing five different screening modalities: namely, screen-film two-dimensional (2D) mammography, clinical breast examination (CBE), breast self-examination (BSE), three-dimensional (3D) digital mammography (such as the Digital Breast Tomosynthesis, or DBT, recently approved by the Food and Drug Administration, FDA), and magnetic resonance imaging (MRI) [55]. Other screening modalities, such as thermography, are still experimental, while tissue-sampling approaches (fine-needle aspiration, or FNA, nipple aspiration or ductal lavage) are usually used for diagnostic purposes only. The USPSTF recommended against routine mammographic screening in women aged 40-49 years, unless the patient's history suggested it and after careful assessment of the benefits and harm. Biennial mammographic screening was recommended for women aged 50-74 years; no evidence of additional benefits or harms emerged with regard to CBE, while BSE was advised against. The USPSTF called for further studies on the clinical usefulness of digital mammography and MRI.

By contrast, the American College of Radiology (ACR), the American Society of Clinical Oncology (ASCO) and the Society of Breast Imaging (SBI) calculated that mammography, if not performed in women aged 40-49 years, would miss 19-33% of cancers and would sacrifice 33 years of life per 1,000 women screened. These

agencies therefore recommended routine screening mammography commencing at the age of 40 years.

A mathematical model seems to support the opinion of the USPSTF [56], since including women in their 40s would increase the number of false-positive cases by 53%. One solution could be the use of ultrasonography [57], which would enable radiologists to detect additional 3-4 cancers per 1,000 high-risk women screened [48]. Moreover, MRI and ultrasound as supplemental screening techniques would be particularly useful for women with extremely dense breasts [48]. However, implementation of this policy should be carefully evaluated by means of a cost-effectiveness analysis, in order to develop the best strategy.

Despite these controversies, breast cancer screening has undoubtedly contributed to reducing cancer mortality by 30-50% [58]. In Italy, after the introduction of organized mammography screening, the IMPACT working group found a statistically significant, steady reduction in the incidence of late-stage breast cancer from the third year onward, with the incidence rate ratio (IRR) declining from 0.81 to 0.71 [59]. This decline was more evident in three regions: Liguria, Tuscany and Lombardy [60]. However, coverage remains low (69.1%) [61].

ANTI-CANCER VACCINES

There are two kinds of anti-cancer vaccines: preventive (or prophylactic) and therapeutic vaccines. The former include anti-HPV vaccines (Gardasil[®] and Cervarix[®]) for the prevention of cervical cancer [62, 63], and anti-HBV vaccines for the prevention of hepatocellular carcinoma [64]. The latter are whole cell-, protein- and peptide-, dendritic cell-, gene-, or idiotypic immunoglobulin-based vaccines [65].

Generally speaking, anti-cancer vaccines stimulate cytotoxic T lymphocytes (CTL) against tumor-associated antigens (TAA) or tumor-specific antigens (TSAs). Therapeutic anti-cancer vaccines have greatly benefited from forward vaccinology [66, 67], which uses advanced mass spectrometry (MS) approaches, thus enabling the design of customized vaccines. Currently, Oncophage[®] and Provenge[®] represent the two most successful approved anti-cancer vaccines.

The autologous heat shock protein (HSP)-based vaccine Oncophage[®] (HSP-peptide complex 96, HSPPC-96) was released in May 2008 in Russia for the treatment of kidney cancer patients at intermediate risk of disease recurrence. Clinical trials conducted among metastatic kidney cancer patients had shown a statistically significant improvement [68]. The second-generation autologous HSP-based vaccine, Vitespen[®], a purified gp96-peptide complex, has yielded promising results in a variety of cancers, including CRC, glioblastoma, lung cancer, melanoma and renal cell carcinoma [69].

In April 2010, the FDA approved Sipuleucel-T (Provenge[®], Dendreon) for metastatic prostate cancer [70]. This vaccine, which elicits CTLs against prostatic acid phosphatase (PAP), is obtained by using leukapheresis, isolating APCs and processing them with PAP

crosslinked to the granulocyte-macrophage colony-stimulating factor (GM-CSF).

Other approved cancer vaccines are Nivolumab (Opdivo[®], formerly known as MDX-1106, recently approved for melanoma and squamous non-small cell lung cancer, currently under clinical trial for further malignancies, including CRC and brain cancer), Ipilimumab (Yervoy[®], approved for melanoma, under trial for bladder and prostate cancer) and Gencicine[®] (approved by the Chinese State Food and Drug Administration or CSFDA for the head and neck squamous cell carcinoma).

Cancer vaccines currently under clinical trial include Tremelimumab (also known as Ticilimumab or CP-675,206, under trial for mesothelioma, bladder cancer), DCvax[®] (for astrocytoma), BiovaxID[™] (Dasiprotimut-T, under trial for follicular lymphoma), ProstVac-VF[®]/Tricom[™] (under trial for prostate cancer), PanVac-VF[™] (a poxviral-based cancer vaccine containing transgenes for the epithelial mucin 1 and carcinoembryonic antigen or CEA, currently under clinical trial for a variety of cancers, including breast and pancreatic tumor), MVax[®] (under trial for melanoma), OncoVax[®] (under trial for CRC), Reniale[®] (under trial for renal cancer) and a glycoprotein-100 (gp100)-based vaccine against melanoma [65, 68], among others.

FUTURE SCREENING PROGRAMS

In many countries, screening tests are also performed for lung cancer, melanoma, prostatic, oral, pancreatic and ovarian cancers. However, their unstructured application has resulted in poor or insufficient scientific evidence [71]. For example, clinical trials such as the European Randomized Study of Screening for Prostate (ERSSP) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [72] yielded conflicting results regarding the utility of Prostate Specific Antigen (PSA)-based screening for prostate cancer, since PSA has not proved superior to digital rectal examination (DRE) [71, 73]. We cannot, however, exclude the possibility that the introduction of more reliable biomarkers, such as MD-miniRNA, which could more effectively distinguish between prostatic hyperplasia and prostate cancer [74], will improve the efficacy of prostate cancer screening.

Further research and high-quality clinical trials are needed. The introduction of new screening programs should be considered only after a careful Health Technology Assessment (HTA) has been performed, and in the light of solid clinical recommendations in conformity with Evidence-Based Medicine (EBM) [75, 76].

FUTURE PROSPECTS AND CONCLUSIONS

In conclusion, prevention programs are an important weapon in the fight against cancer, and currently available evidence shows that they can contribute to reducing both the incidence of cancer and mortality. However, adherence to screening programs remains an issue to be addressed, in that screening tests are still underused [77]. A promising solution could be to personalize screening.

Stratification for population-based risk-adjusted screening programs could be performed by using *ad hoc* risk models. Since cancer is indeed a common complex disease, screening programs could benefit from the use of genomic information, whilst this is generally not so helpful to diagnosis and prediction at the individual level [78]. It is anticipated that merging personal anamnestic data with those from clinical and radiological examinations will give rise to a new discipline, termed radiogenomics, which would optimize personalized medicine by correlating imaging with genetic information [79].

Another scientific hint of the utility of “population-based personalized screening” is the intrinsic biological and genetic difference between screening-detected cancers and interval cancers (that is to say, cancers arising during inter-screening intervals) [79]. Genomics-based stratification could indicate the optimal screening interval. For example, in the field of breast cancer screening, applying genomics and targeting subjects in the top 25% of the risk distribution would include approximately half of all future breast cancer cases [80]. Moreover, one mathematical model showed that a breast cancer screening program based on age and polygenic risk, and which targeted women aged 35-79 years, would reduce the number of false positives, and therefore of unnecessary biopsies and surgical procedures [81, 82].

In order to increase coverage, physicians should strongly recommend screening programs and discuss their patients' doubts and perceived psycho-social barriers [83, 84]. Advocacy could play a major role, and Public Health professionals should discourage opportunistic screening. On the other hand, researchers should develop and investigate new, more acceptable, less invasive tests [37].

New information and communication technologies (ICTs), such as smart-phone applications (known as *apps*), personalized short message services (SMS) and texting [85], could also help to promote adherence to programs. “Screening 2.0” is a great opportunity, which is still underused [86].

In sum, oncology has seen great changes in recent decades; together with improvements in diagnosis and treatment, prevention has played a major role in reducing both the incidence of tumors and mortality. Advances in technology and social media and the discovery of new biomarkers are expected to bring additional benefits.

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Abbreviations

2D: two-dimensional; 3D: three-dimensional; ACIP: Advisory Committee on Immunization Practices; ACOG: American College of Obstetricians and Gynaecologists; ACR: American College of Radiology; ACS: American Cancer Society; APCs: Antigen Presenting Cells; apps: applications for smart-phones and mobile devices; ASCO: American Society of Clinical Oncology; ASCUS: atypical cells of undetermined significance; ASTs: Automated Screening Technologies; BRCA1: Breast Cancer Type 1 susceptibility protein; BRCA2: Breast Cancer Type 2 susceptibility protein; BSE: Breast Self-Examination; CAS: Complex Adaptive System; CBE: clinical breast examination; CCE: colon capsule endoscopy; CDC: Centers for Disease Control and Prevention; CEA: carcinoembryonic antigen; CRC: Colorectal Cancer; CSFDA: Chinese State Food and Drug Administration; CT: computed tomography; CTC: CT colonography; CTLs: Cytotoxic T Lymphocytes; DBT: Digital Breast Tomosynthesis; DCBE: Double-Contrast Barium Enema; DES: Diethylstilbestrol; DNA: deoxyribonucleic acid; DRE: digital rectal examination; DVI: direct visual inspection; EBM: Evidence-Based Medicine; ERSSP: European Randomized Study of Screening for Prostate; FAP: familial adenomatous polyposis; FDA: Food and Drug Administration; FIT: fecal immunochemical test; FNA: fine-needle aspiration; FOBT: fecal occult blood test; FS: flexible sigmoidoscopy; gFOBT: guaiac-based FOBT; GM-CSF: granulocyte-macrophage colony-stimulating factor; HBV: Hepatitis B Virus; HC2: Hybrid Capture 2; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HNPCC: hereditary nonpolyposis colorectal cancer; HPV: Human Papillomavirus; HRC: High-Resolution Colonoscopy; HRT: Hormone Replacement Therapy; HSP: Heat-Shock Protein; HSPCC-96: HSP-peptide complex 96; HTA: Health Technology Assessment; HTTs: High-Throughput Technologies; IBD: inflammatory bowel disease; ICTs: Information and Communication Technologies; IRR: incidence rate ratio; LBC: Liquid-Based Cytology; LMICs: Low and Middle Income Countries; mRNA: messenger RNA; NCDs: non-communicable diseases; P4 Medicine: predictive, preventive, personalized and participatory medicine; PAP: prostatic acid phosphatase; Pap smear: Papanicolau smear; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA: Prostatic Specific Antigen; RCT: Randomized Controlled Trial; SBI: Society of Breast Imaging; sDNA: stool DNA; SMS: Short Message Service; SoSs: System of Systems; STD: Sexually Transmitted Disease; US: United States of America; USPSTF: US Preventive Services Task Force; TC: total colonoscopy; TAAs: Tumor-Associated Antigens; TSA: Tumor-Specific Antigens; VC: Virtual Colonoscopy; VIA: visual inspection using 3%-5% acetic acid; VIAM: visual inspection using 3%-5% acetic acid and magnification; VILI: visual inspection using Lugol's iodine.

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