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Key issues that need to be considered while revising the current annex of the European Council Recommendation (2003) on cancer screening

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Review

The 2003 European Council recommendation urging the Member States to introduce or scale up breast, cervical and colorectal cancer screening through an organized population-based approach has had a remarkable impact. We argue that the recommendation needs to be updated for at least two sets of reasons. First, some of the current clinical guidelines include new tests or protocols that were not available at the time of the Council document. Some have already been adopted by organized screening programs, such as newly defined age ranges for mammography screening, Human Papillomavirus (HPV)-based cervical cancer screening, fecal immunochemical test (FIT) and sigmoidoscopy for colorectal cancer screening. Second, the outcomes of randomized trials evaluating screening for lung and prostate cancer have been published recently and the balance between harms and benefits needs to be pragmatically assessed. In the European Union, research collaboration and networking to exchange and develop best practices should be regularly supported by the European Commission. Integration between primary and secondary preventive strategies through comprehensive approaches is necessary not only to maximize the reduction in cancer burden but also to control the rising trend of other noncommunicable diseases sharing the same risk factors.

Key words: cancer screening, European Union, European Council

Abbreviations: CANCON: EU-wide Joint Action on cancer control; CRC: colorectal cancer; CT scan: computerized tomography scan; ECIBC: European Commission Initiative on Breast Cancer; ERSPC: European Randomized Study of Screening for Prostate Cancer; EU: European Union; FIT: fecal immunochemical test; FS: flexible sigmoidoscopy; gFOBT: guaiac fecal occult blood test; HPV: human papillomavirus; LDCT: low-dose computerized tomography; MS: member states; PBCRs: population-based cancer registries; PSA: prostate-specific antigen; RCTs: randomized controlled trials

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The recommendation of the European Council published in 2003,[1] urging the European Union (EU) Member States (MS) to introduce or scale up breast, cervical and colorectal cancer screening through an organized population-based approach, has had a remarkable impact. Among the age-eligible population of EU in the year 2016, 94.7, 72.3 and 72.4% were residents of the MS that had implemented or planned population-based screening for breast, cervical and colorectal cancers, respectively.[2]

The definitions of the organizational and quality assurance elements incorporated in the Council recommendation have changed over time. It is important to follow recent updates and developments in the concepts of population-based, organized cancer screening and in quality assurance and incremental optimization of programs.[3,4]

Current guidelines recommend new tests or protocols that were not included in the 2003 Council document, like newly defined age ranges for mammography screening, human papillomavirus (HPV)-based cervical cancer screening, fecal immunochemical test (FIT) and sigmoidoscopy for colorectal cancer screening, which have already been adopted for routine use in population-based screening programs in many MS. The current Annex of the Council recommendation, therefore, needs updating, as summarized in the following paragraphs (Table 1). This commentary is a nonsystematic review based on an expert's judgment. The experts contributing to this commentary were involved in reporting the impact of Council recommendation on the cancer screening programs in the EU.[2]

The latest European Guidelines on breast cancer screening[5] published by the European Commission Initiative on Breast Cancer (ECIBC) extended the age recommendation for mammography screening to 45–74 years. There is moderate certainty of the evidence that mammography screening at 45–49 and 70–74 years can reduce breast cancer mortality and the balance between benefits and harms favors mammography screening. Recommendations on digital breast tomosynthesis are contradictory due to the limited evidence currently available.[5,6]

The European Guidelines recommended HPV test as the test of choice for primary cervical cancer screening[7] due to high negative predictive value of HPV tests, the possibility of prolonging the interval between two rounds of (HPV) screening, lower cumulative incidence of CIN 3+ in HPV negative women compared to cytology negative women and the fact that compared to cytology, HPV-based screening is 60–70% more efficacious in preventing invasive cervical carcinomas.[8] Several MSs have already introduced HPV test for primary screening followed by triaging with cytology.

The European Guidelines on colorectal cancer (CRC) screening[9] have identified FIT as superior to guaiac Fecal Occult Blood Test (gFOBT) with better detection rates, higher positive predictive values and logistic advantages. In addition, a multicenter trial in the United Kingdom demonstrated substantial benefit for a single round of screening of individuals aged 55–64 years with flexible sigmoidoscopy (FS) and the benefit was maintained over 17 years.[10] A significant reduction in incidence of colorectal cancer was demonstrated in the screened population both in the intention-to-treat (reduction by 26%) and the per-protocol analyses (reduction by 35%). The intervention group had 30 and 41% reduction in mortality from CRC in intention-to-treat and per-protocol analyses, respectively. A pooled analysis of two other European randomized controlled trials (RCTs) and one American RCT demonstrated a small but statistically significant protective effect of FS screening for proximal cancer (incidence reduction by 14%) at 12-year follow-up. This analysis demonstrated the protective effect of screening on reduction of both CRC incidence and mortality among men and women younger than 60 years. More effective alternative methods may be required for women above 60 years of age to detect the proximal lesions in particular.[11] On the other hand, the UK trial with 17 years of follow-up has reported very similar effects against colorectal cancers by both genders and age groups, but no or very little impact on proximal cancers.[10] Although the results from RCTs evaluating CRC screening using colonoscopy are awaited, colonoscopy can be expected to be at least as effective as FS, with potential added value to early detect proximal lesions.

Table 1. Key issues and recommendations that need to be considered while revising the current Annex of the Council Recommendation (2003) on cancer screening

Cancer site	European Council recommendations 2003 on cancer screening	Issues to be considered in revised recommendation
Cervical cancer	Screening with Pap smear starting at age 20–30 years	Adopt HPV-based cervical cancer screening with appropriate interval and age range
		Adopt appropriate management strategies for screen-positive women
		Define appropriate screening policies following the introduction of HPV vaccine in immunization programs
Breast cancer	Mammography screening in women aged 50–69 years	Mammography screening in women aged 45–74 years
		Wait for more conclusive evidence on the use of tomosynthesis for breast cancer screening
Colorectal cancer	Screening with fecal occult blood test in men and women aged 50–74 years	FIT for age 50–74 once every 2 years or flexible sigmoidoscopy once in a lifetime for colorectal cancer screening
		Wait for more conclusive evidence on screening once in a lifetime with colonoscopy
Lung cancer	No recommendation	Wait for more conclusive evidence on lung cancer screening with LDCT for heavy smokers aged between 55 and 74 years, taking into consideration resource implications, cost-effectiveness and harms
Prostate cancer	No recommendation	Wait for more conclusive evidence on prostate cancer screening taking into consideration harms to benefits ratio
		Monitor opportunistic testing

Abbreviations: FIT, fecal immunochemical test; HPV, human papillomavirus; LDCT, low-dose computerized tomography.

The outcomes of the RCTs evaluating screening for other cancer sites including lung and prostate cancers have been published recently.

Annual screening with low dose Computerized Tomography scan (LDCT scan) of heavy smokers aged between 55 and 74 years can achieve a significant 20% reduction in lung cancer mortality in settings where very high-quality radiology services are available and dedicated facilities exist to investigate and manage screen-detected pulmonary lesions.[12,13] The benefits need to be carefully balanced against the possible harms of false-positive diagnosis (approximately 20% of the screened population will have suspicious nodules in the lungs and approximately 80% of these are benign lesions). Further reported harms include complications of pulmonary needle and surgical biopsy (reported rate of major complication from such procedures is 0.4%) and overdiagnosis (National Lung Screening Trial in the United States of America reported that 18.5% cases were overdiagnosed relative to screening with chest x-ray during trial period).[14] In the Netherlands, the Nelson trial showed that[15] computerized tomography (CT) scan decreased lung cancer mortality by 26% in high-risk men and 39% in high-risk women over a 10-year period.[16] Yet, the logistics of setting up such a complex program and the cost-effectiveness of lung cancer screening need to be carefully considered prior to decision-making. Needless to say, prevention of smoking and ensuring access to smoking cessation services should be the priority to reduce lung cancer and other smoking-related cancers in all MS.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) evaluating prostate cancer screening in men aged 55–69 years with the prostate-specific antigen (PSA) test every 2–4 years found a 21% reduction in the relative risk of prostate cancer mortality.[17] This corresponds to one less death from the cancer per 781 men invited for screening. Harms that have been reported include complications of biopsy (1/1,000 screened men reported sepsis after prostatic biopsy) and significant treatment-related complications (3/1,000 screened men reported urinary incontinence and 25/1,000 screened men reported erectile dysfunction after treatment).[18] Overdiagnosis is also a major harm of prostate cancer screening. A pragmatic recommendation at the EU level is necessary to provide guidance to the Member States to tackle the huge burden of prostate cancer in men. Opportunistic prostate cancer screening alongside PSA testing in men with urinary dysfunction (or possible other nonspecific symptoms of prostate cancer) is widely spread in EU member states,[19] often with unknown quality of testing, diagnostic process and management history. Monitoring these practices is important in order to reduce the side effects of inappropriate testing and referral.

In the future, the Council should consider recommending more stringent legal frameworks, governance and quality assurance structures, taking into account that only little development has been reached in some MSs with serious barriers to effective population-based cancer screening 15 years after the recommendation of 2003.[20] Existing legal frameworks often miss adequate implementation, monitoring and evaluation of screening program services and their systematic quality assurance, as demonstrated in surveys on cervical cancer screening.[21,22]

Monitoring and evaluation of the performance and the outcomes of screening—including harms—conducting appropriate surveillance alongside a synthesis of evidence and assessing the criteria for decision-making should be recommended as a regular and continuous activity in order to improve the quality, enhance the benefits and minimize the harms. The periodic analysis and reporting of the performance of the population-based cancer screening programs and opportunistic activity adopted by EU Member States is of great public health significance and should be sustained. The updating of the status report on cancer screening in EU should be periodic, at regular intervals (1–3 years) following the data collections timeframe of screening programs.

Data collection tools, protocols and outputs can be further standardized and made available through an interactive, web-enabled platform.[21] Information on the organizational details, disease burden, prioritization, as well as on the evaluation studies on benefits and harms should be added to the reporting system. These will be valuable resources for program managers, clinicians, policy makers, researchers and public at large. Adequate communication should ensure proper informed consent or denial by the persons offered screening.

The new recommendation should clarify the need to ensure consistency and enhance quality of the data collected for the screening reports and studies. The great variability of the performance indicators observed across the MS can be explained not only by the different referral criteria, previous opportunistic testing, diagnostic tests of the symptomatic population, quality of screening and of diagnostic tests and different background incidence, but also by different systems of documentation and reporting.

Reference standards for quality and process indicators of the screening programs at the EU level should be developed and adopted, starting from achievable performances of well-established screening programs. Enlisting minimally acceptable standards for the core indicators will greatly support new programs to organize their strategies and quality assurance plan. It is also essential to record and score the harms (and not achieved benefits), which are associated with poor performance. Adoption of reference standards at the EU level will require standardization of the definitions and the classifications.

The second EU Cancer Screening Report highlighted the importance of regular linkage of data collected within cancer screening with National Health Interview Surveys and population-based cancer registry to obtain more precise information on attendance and intervals in opportunistic and population-based screening settings, as well as outcome, for example, cancer diagnosis and cancer characteristics. Official contacts should be promoted with national institutes of population sciences and statistics to introduce specific questions on cancer screening frequency and intervals, if not already

included, and to standardize definitions and data collection procedures at the EU level.

Population-based cancer registries (PBCRs) provide valuable information on the quality of cancer screening programs by documenting the impact on cancer-specific incidence, stage distribution, cancer management including treatment and excess mortality.[23] PBCRs should be strengthened in countries already having population-based screening programs or are contemplating to introduce them.

The results of the second EU Cancer Screening Report as well as of the EU-wide Joint Action on cancer control (CANCON), have pointed out remarkable barriers and social inequalities in access to cancer screening.[2,20,24] The coverage of existing programs needs to be further expanded to reduce inequalities in participation and access to benefits all specifically the hard-to-reach groups within the population. To find appropriate solutions to these barriers, European research collaboration is required between various screening centers and programs.[20] Moreover, inequalities in health extend well beyond differences in attendance to the screening program, up to differences in awareness, risk factors, access to cancer care and to health care in general.

Integration between primary and secondary preventive strategies through comprehensive approaches is necessary not only to maximize the reduction in cancer burden but also to control the rising trend of other noncommunicable diseases sharing similar risk factors. Embedding primary prevention interventions into the screening setting can also act as a positive reinforcement for the taking charge effect that occurs during participation in the screening programs. Integration of primary and secondary prevention is particularly important for cervical cancer as in many EU countries the first cohorts of women vaccinated against HPV are already being screened. Defining appropriate screening policies for these highly vaccinated birth cohorts is essential in order to avoid waste of resources and unjustified harm. Primary prevention strategies for lung cancer, including reduction of demand for tobacco products and access to them, are highly effective and should be prioritized over screening for the disease.

In order to make the most of the "teachable moment" offered by the screening setting, every screening visit should be utilized as an opportunity to disseminate prevention messages that are coherent and evidence based in all the European Countries. It is essential that prevention interventions are cost-effective and consistent with the 12 recommendations of the 4th edition of the European Code Against Cancer.[25] In addition, CANCON[26] has considered criteria important for the national and EU-level decision-making on cancer screening programs.

There is a large variation in the financial resources available for health care within the EU MS. The cancer screening programs are generally resourced intensive and highly demanding on personnel resources, information technology and infrastructure. These pose challenges in assessing the threshold values of what is cost-effective within the EU countries.[20] Resource constraints may prevent adequate systematic screening evaluation and monitoring which may further feed on nonefficient program. Tailored screening strategies for limited resources settings need to be developed, and these strategies must be taken into account in all future European recommendations on cancer screening.

The positive impact of the Council Recommendation in encouraging implementation of complex population-based programs reaching large segments of the European population with highly specialized multidisciplinary services integrating a broad range of health care providers, regulators and other institutions should be taken into account in future efforts to improve the control of cancer and other noncommunicable diseases in the EU.

Conflict of interest

J.D. declares being a former recipient of research grants from Merck/SPMSD to institution on the subject of long-term registry follow-up of vaccine impact in populations and HPV surveillance. For the remaining authors, there are no conflicts of interest.

Disclaimer

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