

EARLY DETECTION IN CANCER: EARLY DIAGNOSIS AND SCREENING

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Early detection, which is a part of preventive medicine, can be defined as follows: *“All kinds of health services practiced targeting the entire healthy community or the section of the community assumed to be at risk, in order to detect a certain disease at the beginning of the duration of the disease, before symptoms and indications of the disease emerge.”*

The concept of early detection has two components: **early diagnosis** and **screening**. (a) Early diagnosis: Ensuring that individuals present to health institutions before the symptoms and indications of the disease emerge by training both the public and the physicians and other health personnel. (b) Screening: Identifying the disease at an early stage by subjecting individuals who appear healthy but are at risk to an appropriate method of examination, if such a method exists. Cancer screening methods can be divided into three groups with respect to application means: (a) Opportunistic screening, (b) Community based screening, (c) Screening service.

The first widespread cancer screening method has been cervical cancer screening by “Pap smear”. It is believed that these implementations account for the decrease observed in the mortality rate of cervical cancer after the 60’s in various countries.

Several studies have demonstrated that community-based mammography screening, when implemented at the appropriate age groups, at appropriate intervals and ensuring quality assurance at each step, reduces female breast cancer mortality by up to 30%.

Colorectal cancer that can be screened by faecal occult blood test is one of the three cancer types recommended by the European Union for screening.

In general, widespread usage of prostate cancer screening using the PSA (prostate-specific antigen) test has not yet been largely accepted yet. The European Union maintains the opinion that accurate results can only be achieved in 2008 regarding this issue.

What is early detection?

Traditional medicine takes care of individuals who present to a physician, with the symptoms and indications emerging in himself; the aim is first to name the disease, that is to decide on a **diagnosis**, then to **treat** the individual, the disease of whom has been identified, in the most appropriate way and to have him back to his normal health condition.

The target population of *preventive medicine* is healthy people; the aim here is first to find the factors leading to a disease or increasing the risk of a disease, and then to prevent these factors to make healthy individuals into sick individuals, that is to **protect** the individual.

Early detection, which is a field of preventive medicine may be defined as follows: “All kinds of health services practiced targeting the entire healthy community or the section of the community assumed to be at risk, in order to detect a certain disease at the beginning of the duration of the disease, before symptoms and indications of the disease emerge.”

The rationale underlying early detection studies is this: “If abnormal findings are identified in an early stage in some diseases, such diseases may be eliminated much more easily, with less expenditure and less disturbance on the patient; thus, the burden that such a disease places on the public may be reduced more easily.”

The two important points to be considered in early detection are:

1. If the patient will not benefit from detection at an early stage for a certain disease, early detection is not recommended. For instance, within the framework of currently available methods, detection of Alzheimer’s disease before symptoms and indications appear in an individual will not bring any medical benefit, on the contrary, such an information will be a source of psychological concern for the individual and his/her relatives and friends.

2. Before launching an early detection program, the conditions and requirements to ensure that the objective of the program is achieved should be guaranteed. In other words, how to reach a definitive diagnosis in individuals identified as “suspected” during screening and how to treat those who are diagnosed to have the disease should be planned at the start. For instance, if there is no opportunity to have the individuals who are identified to have a visual disability examined by an ophthalmologist and to provide them spectacles, it is best not to launch a visual disability screening program at all.

The two components of early detection

The concept of early detection has two components, namely **early diagnosis** and **screening**:

1. **Early diagnosis:** To ensure that individuals present to health institutions before symptoms and indications of disease appear by training both the public and the physicians and other health personnel.

2. **Screening:** To detect a disease at an early stage through applying an appropriate method of examination, if there exists one, to individuals who appear healthy but are at risk.

Early diagnosis activities are generally carried out as campaigns targeting the public. When planning an early diagnosis program, factors such as training of health care professionals, and reorganisation of the diagnostic and treatment establishments to meet the representations.

Many of the “invited individuals group” are healthy persons. This group has different properties compared to the “individuals presenting to a clinic with a complaint group”. Not only those who present, but also the methods used in screening are different than the clinical diagnosis methods. A diagnosis for an individual can not be reached with screening methods; they can only be recognised as “suspected cases”, i.e. as individuals with atypical findings, they are recalled and identified as “healthy” or “patient” using clinical methods.

Screening criteria

The ten principles, disclosed in a monograph of the World Health Organisation, concerning for which disease or health condition applying screening should be appropriate are still valid (Wilson and Jungner, 1968) (1 – 3). These principles, which should be taken into account when planning a cancer screening program, are as follows:

1. The condition being investigated should be an important health problem.

2. There should be a recognised treatment for the patients of the identified disease.

3. Facilities for diagnosis and treatment should be available.

4. The condition should have a defined latent or early symptomatic stage.

5. There should be a suitable test or examination method for the condition.

6. The test should be acceptable to the population.

7. The natural history of the disease, including development from latent to a declared disease, should be adequately understood.

8. There should be an agreed policy as to whom to regard as patients.

9. The cost of case-finding (including diagnosis of patients and treatment of the diagnosed patients) should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case-finding should be a continuous process, not just a "once and for all" project.

In cancer screening, in addition to these, the strategy and the modality to be selected should have been proven to reduce the burden of cancer in the society.

Role of early detection in cancer control

Many diseases, the common properties of which is unusual cell proliferation, are grouped under the heading, *cancer*. Consequently, *cancer burden* means all the costs paid by the society due to this disease group, such as diseases, deaths, economic loss, social damages, etc.

The number of new cancer cases in the world in one year has been estimated to be around 11 millions totally for 2002 (approximately 6 million males, 5 million females). In the same year, number of deaths due to cancer has been calculated to be 7 millions totally (around 4 million males, 3 million females) (4). Currently available early detection methods provide us the opportunity to prevent about one third, i.e. 2 - 2.5 million deaths due to cancer annually, yet it should no doubt be forgotten that this number is based on a hypothetical calculation (5). Again hypothetical calculations show that in this century deaths due to cancer will exceed the deaths due to cardiovascular diseases, and cancer will occupy the first place in causes of death (3).

Aims of public health for cancer are to define the cancer burden in a society in terms of incidence, mortality and similar indicators; to develop strategies against common cancers; and to relieve the burden of cancer on the society, directing the resources of the society to implement such strategies. Integrating such efforts actively may be possible by a cancer control program, prepared and implemented for a certain society.

In general, there are four components of a cancer control program (5):

- In *primary prevention*, strategies for prevention of various cancers, particularly lung cancer; for example “control of tobacco addiction”,
- *Secondary prevention* means the strategies under the heading early detection, including early diagnosis and screening,
- *Tertiary prevention* strategies are developed to employ appropriate diagnosis and treatment methods to individuals with symptoms and findings,
- Efforts to increase the quality of life of patients especially via pain control are termed as *palliative care*.

An early detection strategy should be implemented as a component of a cancer control program specific to a region or a country.

Early diagnosis and community screening in cancer

Each disease under the heading cancer has its specific characteristics. Each type of cancer has a specific aetiology, risk factors, methods of diagnosis and treatment modalities. Therefore, early diagnosis and screening strategies are recommended for some cancers, whereas not recommended for others. On the other hand, the components of cancer burden, and the methods and technologies used may change from one year to another; consequently, recommendations concerning early diagnosis and screening may also change in time. Furthermore, it should not be forgotten that the general recommendations of international organisations must be re-assessed in connection to the conditions of each country.

Early diagnosis programs for relieving the cancer burden on the society should be considered together with campaigns that aim reducing the exposure of individuals to risk factors, i.e. primary prevention. For instance, in Australia, where the mortality rate of skin melanoma is higher than many other countries, a sound program is being carried out for the control of this cancer. This program covers both comprehensive training campaigns to lessen exposure to sun's rays, which has an important role in the aetiology of this cancer, and organisation of "skin clinics" where service is given free of charge by specially trained primary health care physicians. Another example is found in cervical cancer; with widespread use of the vaccination against the HPV factor, determined to be related to cervical cancer, cervical cancer screening and vaccination programs will have to be assessed together.

Raise of awareness among physicians, nurses and other health care professionals, as well as among the society will have important impacts on reducing deaths by early detection. Although the implications for different age and sex groups will be different, some indications that should be taken into account and that might be stimulators for some cancers are masses, non-healing wounds, unusual bleedings, persistent indigestion, chronic dysphonia, etc. Cancers with which early diagnosis are specifically related are breast, cervical, mouth, larynx, colon-rectum and skin cancers.

Under the light of existing data, the World Health Organisation holds the opinion that massive population based screenings should only be advocated in countries which have the resources to conduct screening programs covering a large proportion of the population, and for:

- a. Breast cancer using mammography,
- b. Cervical cancers using cytology.

In the guidelines published by the World Health Organisation, **National Cancer Control Programs**, the following recommendations are given concerning for which cancers early diagnostic strategies and screening programs should be implemented (5):

1. *Cancers for which both early diagnosis and screening strategies are recommended to be implemented:* female breast cancer, cervical cancer.

2. *Cancers for which early diagnosis strategies are recommended to be implemented, but screening strategies are not:* oral cavity cancers, nasopharyngeal cancer, stomach cancer, colorectal cancers, skin melanoma, non-melanoma skin cancers, ovary cancer, bladder cancer, prostate cancer.

3. *Cancers for which both early diagnosis and screening strategies are not recommended to be implemented:* esophagus cancer, lung cancer, liver cancer.

On the other hand, in the Council Recommendation on cancer screening published by the European Union in 2003, it is noted that effectiveness of screening have been demonstrated in colorectal cancers besides breast cancer and cervical cancer in women, and that the outcomes of the studies which will show whether screening is effective in prostate cancer are expected to become available in 2008 (6).

Types of cancer screening

Whatever the cancer type is, cancer screening can be grouped into three depending on the way of implementation:

1. Opportunistic screening: This can be thought of as a part of early diagnosis activities. In general, in studies based on population, who will participate in which screening program is announced and it is expected that the group who appear healthy but are at risk present themselves to the institutions carrying out the screening activity. Here, the names of the target population are not identified and invited individually. For example, the effectiveness of opportunistic screening for breast cancer have not been demonstrated yet, however, it can be said that awareness is raised in the public through such screening types. Another important point is that in communities where opportunistic screening is widespread, participation appears to be low when a community-based screening program is implemented.

2. Community-based screening (community screening): The starting point here is the group which lives in a certain geographical or administrative region and which is at risk. Since the goal here is to screen the entire group, the population under risk, called the “target group”, is determined, the names are identified, and persons are invited for screening individually. In order for a community based screening be effective, it is necessary that quality assurance be ensured at all stages,

and a high percentage of the target population be screened. If, in a community, for a given cancer,

a. Mortality, incidence, prevalence data are high, and

b. The infrastructure is adequate, both in administration and human power as well as equipments and tools,

it may be advised that programs for screening the entire target population at risk in given regions or countrywide are implemented. There are two cancer types, for which the reduction in mortality rate by screening programs has been proven: breast cancer in women (mammography screening) and cervical cancer (“pap-smear” screening). In recent publications, it is reported that favourable results are taken in colorectal cancers with faecal occult blood or colonoscopy screening in population aged 50 or older.

3. Screening service: Screening service is conducting cancer screening throughout the entire country, within the system that provides health care services. A typical example of such a practice is the United Kingdom; in the entire UK, breast cancer screening by mammography and cervical cancer screening by Pap smear is being implemented since 1988, and recently, pilot studies has been launched for colorectal cancer (7).

Assessment of cancer screening

1. Choice of the screening test to be used

A technique used in the clinic for diagnosis becomes a different tool when it is used for screening. For example, practice of *clinical mammography* and *screening mammography* are similar; however, there are also significant differences between these two, and in trainings such differences should be underlined. Clinical mammography has to be directed to the subject being examined, together with the symptoms and indications. On the other hand, in screening mammography, the most important finding that should not be overlooked is **microcalcifications**, i.e. the *small killer white spots*. From this point of view, clinical mammography can be compared to “boutique shops” while mammography screening is like “prêt-à-porter” in clothing sector: Despite the similarities in appearances of dresses, there are big differences between several facets of those two systems producing the dress, namely devices used, infrastructure established, vocational training, after-sales service, etc.

No **screening test**, i.e. *examination used for screening* can say “no disease” for all healthy persons in the population; no screening test can detect all patients, and it has no such goal. Nevertheless, such properties of screening tests can be measured and can be compared with each other in this respect. The more patients a test can discriminate among the “actual patients” in the target group as suspects, the higher is the **sensitivity** of that test. The sensitivity of a test is calculated from the “the number of suspected cases identified in 100 actual patients” and is

expressed as percentage. On the other hand, the percentage of persons identified as “not suspected” among healthy persons by a test is the **specificity** of that test.

Specificity and sensitivity together determine the **validity of a test**. If when using a given test the threshold is lowered to increase the sensitivity, i.e. more persons are identified as “suspects”, the specificity of the test will decrease, i.e. more healthy individuals will have to be subjected to further examination. On the contrary, if in a screening “suspected” individuals are chosen more meticulously, the specificity of the test will increase, but its sensitivity will decrease, i.e. less patients can be detected.

2. Bias:

Every reduction in cancer cases observed in the population after a screening program is not a real reduction; i.e. biases that should be taken account in screening studies have been defined. The three most important are:

a. **Lead time bias:** The cases detected during screening are most possibly cases that would have been diagnosed after some time by clinical symptoms. Thus, although the time of death does not actually change, the survival time of the cases determined by screening will appear to be relatively longer. Therefore, the outcome of the screening should be measured in terms of decrease in mortality rate, rather than extension of the survival time.

b. **Length bias:** Let us say that a disease has two types: In the mild type, the patients live longer, and in the severe type shorter. Since the long survivors shall be more likely to be detected by a periodical screening program, the survival time of the patient group detected by screening will be longer than the survival time of all patients. Therefore, when assessing the screening test, mortality should be measured rather than survival.

c. **Over-diagnosis:** It does not mean that every case detected through screening will necessarily become a clinical case; for example, some of the cases in the in-situ stage will never attain the invasive cancer stage. Consequently, such individuals will not be covered by the mortality rate calculations of clinical cases, but will be covered in the mortality rate calculations of the cases screened, thus, rate will be reduced artificially. To eliminate such bias, it is recommended that only the reduction in the mortality rate of invasive cases to be taken into account.

3. Measure for successful results:

As the measurable goal of cancer screening is reduction of cancer mortality, the real measure of a successful screening is the decrease observed in cancer mortality rate in the screened community. However, years have to pass to observe this decrease. Thus, to be able to quantify the success of a screening program in shorter time, operational criteria

such as *coverage rate, participation rate, recall rate, percentage of interval cancers* in all cancers.

Probable damages of cancer screenings

When planning a cancer screening program, the probable damages that the program may cause should be taken into account besides the benefits. Such probable damages may be as follows:

1. Many of the screening examinations are simple, easily applicable tests with very few **unwanted results**. Nevertheless, adverse results which are immediately observed (such as intestine proliferation during colonoscopy) or are observed later (increase of cancer risk due to radiation received) must be taken into account.

2. Individuals who were identified as suspects during but were not diagnosed as cancer as a result of further examinations (i.e. individuals whose screening test result is a **false positive**) might be subjected both to unnecessary medical intervention (dissection of benign masses due to suspicion of breast cancer) and to unnecessary anxiety.

3. No screening test can have capacity to detect all cases, i.e. it is inevitable that some cases are overlooked (**false negatives**); since such individuals will be announced healthy, they will be assured by mistake.

4. Another result, named as **over-diagnosis** is as follows: It is not necessary that the symptoms detected in individuals by screening will appear as cancer in all cases. For example, it is well known that in breast cancer screenings, at least some of the cases detected at the **in situ** stage, that is when cancer has not yet crossed the basal membrane, will never become clinical cancer during the life-time of the individual. Thus, it can conveniently be said that some of the interventions made after screening are actually unnecessary.

When launching a screening program, the **alternative cost** of the screening should also be considered. Certain sources will be expended in the screening; if there were no screening, these sources could have been used elsewhere. Upon deciding on a screening program, such alternatives are waived. When confronted with such a comparison, a public health specialist wishes to implement the strategies that will reduce the cancer burden on the society most with the available sources.

A very good compilation of publications of actual cancer screenings can be found on the Internet on the *Physician Data Query (PDQ)* web site prepared by the **USA National Cancer Institute (NCI)**. This data base compiling the results of scientific publications is frequently up-dated (8).

Cervical cancer screenings

Cervical cancer is one of the female cancers frequently observed. For this cancer, annual number of cases is calculated to be 493 thousands and the deaths 274 thousands worldwide. The annual number of cases estimated for Turkey is almost 1,400, and deaths about 730 (in 2002) (4).

In recent years, a close relation has been determined between the infections caused by some types of the *Human Papilloma Virus*” (HPV) in females and cervical cancer. This relation explains why having multiple sex partners and bad hygiene conditions are important risk factors for this cancer. Satisfactory vaccination studies implemented in recent years have given way to great hope for preventing HPV infection and cervical cancer in new generations, but currently screening continues to be the most important strategy in preventing cervical cancer.

The first widespread cancer screening has been cervical cancer screening by “Pap smear”. The Pap-smear technique can be summarized as taking a smear from the cervix with a spatula and examining the cells in this smear under the microscope. This screening method, developed by the Greek scientist **Georgios N. Papanicolaou** and named as “**Pap-smear**” in reference to the name of this researcher, has been rapidly adopted since it is cheap and easy, and since it did not lead to any serious complication, and has found widespread use in the second half of the twentieth century. It is believed that these implementations account for the decrease observed in the mortality rate of cervical cancer after the 60’s in various countries (9).

Breast cancer screenings

In many countries, the most frequent cancer type in women is breast cancer; it is being estimated that worldwide annual number of new cases exceeds 1 million 150 thousands, and that every year more than 400 thousand women die because of this cancer. In Turkey also the estimated annual number of new cases is close to seven thousand and deaths close to three thousand (in 2002) (4).

That breast cancer in women meets the pre-conditions required for screening was determined years ago; discussions and research concerning cancer screening has focused primarily on this cancer type (10).

There are three modalities that may be applied in breast cancer screening: (i) *To train women in breast self-examination*, (ii) *To conduct periodical clinical breast examinations*, and (iii) *To take periodical mammography*. Various studies have demonstrated that community-based mammography screening, when implemented at the appropriate age groups, at appropriate intervals and ensuring quality assurance at each

step, reduces female breast cancer mortality. That the first two modalities reduce mortality has not been proven yet, even when they are implemented as community screening; however, regarding raising awareness in the society, implementing these modalities as a part of early diagnosis efforts is being recognised as appropriate.

It is well known that in a population, in order to be able to reduce breast cancer mortality by 30% through mammography screening, such screening should be community-based, participation should exceed 70%, such screenings should be continued for years, and quality assurance should be provided at every stage of the program. The most comprehensive source on quality assurance of breast cancer screening programs has been published by the working group of the European Union (11).

International organisations have differing recommendations concerning to women of which age group should mammography be applied, and at what frequency; the most appropriate is every country should develop standards according to its own conditions. In the standard developed by the Cancer Control Department of the Ministry of Health for Turkey, accessible on the internet, it is advised that women of the 50 – 69 age group have bilateral mammography taken every two years (12). This age group is specified for women without any particular risk with respect to breast cancer, in case of carrying an individual risk, the age is not considered and the time distance between mammograms should be determined by clinician.

Since having breast cancer in close relatives is an important risk factor for a woman, it may be recommended that this group is more frequently monitored. However, it will not be appropriate to organize a screening programme only for the relatives of known breast cancer cases because of the lack of resources or some other reasons since such a screening programme will be able to access only 7-10% of cases.

Colorectal cancer screenings

Colorectal cancers (cancers of the large intestine) are among frequent cancers; the annual number of cases for this group of cancers is 550 thousand in men and 472 thousand in women, and the annual number of deaths are calculated as 278 thousand in men and 250 thousand in women. The annual number of cases estimated for Turkey exceeds 5,000 (approximately half of this number are men and the other half are women), the annual number of deaths are about 3,300 half being men and the other half women (in 2002) (4).

Like the other gastrointestinal cancers, risk factors related to diet have been identified in colorectal cancers, for example, the preventive effect of eating fresh vegetables and fruits is already known; however, it has not been demonstrated that the mortality of these cancers can be

reduced by a primary prevention strategy such as intervention to diet and thus, early detection strategies for colorectal cancers continue to be important. Since colorectal cancers mostly develop from benign polyps and since such development takes time, it is believed that screening may be effective.

As screening modalities, the followings are recommended: (i) *Periodic examination of faecal occult blood*, (ii) *Periodic sigmoidoscopy examination*, (iii) *Sigmoidoscopy examination in intervals together with annual examination of faecal occult blood*. These methods have been tested through various studies and promising results have been obtained in age groups of over 50 for both sexes for each of these two modalities. However, in wide programs generally examination of faecal occult blood is being used.

Recently, in 2007 in the United Kingdom and Canada colorectal cancer screening programs were launched. Colorectal cancers are one of the three type of cancers recommended by the European Union for screening (6-7, 13).

Other cancers and screening possibilities

Various screening strategies have been tried for a number of cancer types especially for which primary prevention strategies have not been developed; however, many of these have not been successful. For example, for lung cancer which is the cancer type that causes the highest number of deaths, various imaging techniques have been tried as screening tests since 1950's, starting with lung graphy, but it has not been possible to reduce the mortality of this disease with any modality.

When in 1990's markers were found, it was thought that screening possibilities for some cancers would increase; for example screening by CA 125 for ovarian cancer, for which screening with pelvic examination and ultrasonography was not successful was used, but a successful result could not be achieved in the population. Today, ovarian cancer screening with CA 125 is only recommended for high risk groups.

In battle against prostate cancer, the incidence of which has been increasing due to ageing of the population in many countries, a new method, **prostate specific antigen (PSA)** has been suggested as a screening method, and in various countries prostate cancer screenings has been carried out examining this antigen. Screenings in age groups of 50's and 60's are more promising than those conducted in age groups of 70 or more; however, when assessed wholly, the outcomes of the studies are contradictory and widespread use of prostate cancer screenings has not yet been widely recognised. The European Union holds the opinion that accurate results regarding this matter can only be obtained in 2008 (6).

There is no screening method suggested for testis cancers, which develop at relatively younger ages and which is treated easily, but early diagnosis studies are being suggested.

For oral cavity cancers widespread in India and East Asia, visual inspection of the oral cavity in such regions is suggested as a cheap and easy screening method.

For skin melanoma, which is the most fatal type of skin cancers, periodical visual inspection was suggested as a screening method, but the experiences of countries such as Australia and New Zealand demonstrate that to establish an organisation at primary health care level and training of physicians are more effective.

Apart from screening in the general population, there are cancer screenings that are suggested to be conducted in narrower groups having a risk factor. For example, patients with Barrett oesophagus should be followed up with regard to oesophagus cancer. Besides these, for cancers, the incidence of which are high in some countries, screening programs specific for that country are being implemented, such as oesophagus and liver cancer screenings in China and stomach cancer screening in Japan.

Cancer screening in Turkey

In Turkey, early diagnosis and screening activities for cancer are executed under the coordination of the Cancer Control Department of the Ministry of Health. The Department, knowing that the existing institutional infrastructure in Turkey is not adequate in conducting widespread cancer screening, has started a new organisation that will operate for this goal in the 1990's.

It was thought that these new centres, integrated to hospitals in administration, would carry out screening for breast and cervical cancers, and would become institutions of cancer control within primary health care services. At least one such centre is planned to be established in every province, and in these centres, the number of which are increasing, opportunistic screenings are carried out besides public education and clinical examination. The first two centres which have completed systematic breast cancer screening are Narlıdere (İzmir) and Balıkesir.

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