First Report of Screening an Asymptomatic Population for Cancer: the Yield of an Integrated Cancer Prevention Center

Ben Boursi MD[1], Hanan Guzner-Gur MD[1], Yaquv Mashich MD[2], Udi Miler MD[3], Eyal Gur MD[3], Roy Inbar MD[4], Arye Blachar MD[5], Fanny Sperber MD[5], Shlomi Kleiman MD[6], Ariel Yafo MD[7], Hanoch Elran MD[8], Tal Sella BSc[9], Inna Naumov MSc[9], Diana Kazanov MSc[9], Sarah Kraus PhD[9], Lior Galazan BSc[9], Netta Reshef BSc[9], Tali Sion-Tadmor BSc[9], Miri Rozen[9], Eliezer Liberman MD[9], Menachem Moshkowitz MD[9] and Nadir Arber MD[9]

Departments of [1]Medicine B, [2]Dermatology, [3]Plastic Surgery, [4]Surgery A, [5]Radiology, [6]Oral and Maxillofacial Surgery, [7]Obstetrics and Gynecology and [8]Neorosurgery, and the [9]Integrated Cancer Prevention Center, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Cancer is a leading cause of mortality worldwide. The most effective way to combat cancer is by prevention and early detection.

Objectives: To evaluate the outcome of screening an asymptomatic population for the presence of benign and neoplastic lesions.

Methods: Routine screening tests for prevention and/or early detection of 11 common cancers were conducted in 300 consecutive asymptomatic apparently healthy adults aged 25–77 years. Other tests were performed as indicated.

Results: Malignant and benign lesions were found in 3.3% and 5% of the screenees, respectively, compared to 1.7% in the general population. The most common lesions were in the gastrointestinal tract followed by skin, urogenital tract and breast. Advanced age and a family history of a malignancy were associated with increased risk for cancer with an odds ratio of 9 and 3.5, respectively (95% confidence interval 1.1–71 and 0.9–13, respectively). Moreover, high serum C-reactive protein levels and polymorphisms in the *APC* and *CD24* genes indicated high cancer risk. When two of the polymorphisms existed in an individual, the risk for a malignant lesion was extremely high (23.1%; OR 14, 95% CI 2.5–78).

Conclusions: Screening asymptomatic subjects identifies a significant number of neoplastic lesions at an early stage. Incorporating data on genetic polymorphisms in the *APC* and *CD24* genes can further identify individuals who are at increased risk for cancer. Cancer can be prevented and/or diagnosed at an early stage using the screening facilities of a multidisciplinary outpatient clinic.

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KEY WORDS: cancer, prevention, early detection, screening, genetic polymorphisms

OR = odds ratio
CI = confidence interval

The annual estimated incidence of cancer in Israel is 23,500 new cases per year; the prevalence is 120,000 for a population of 7 million inhabitants and the mortality rate 10,000 annually (unpublished data of the Israel Cancer Association). One of the most effective ways to combat cancer is by means of a program of prevention and early detection. Different screening methods and simple lifestyle modifications have been postulated to reduce cancer risk, morbidity and mortality [1,2], but little is known about the potential beneficial effects and harms of screening asymptomatic populations for occult cancers. In addition, the role of screening for genetic polymorphisms related to cancer in asymptomatic healthy adults has not been defined. Japan is the only country that has an organized cancer screening program for people over the age of 40, which has increased the detection rate of potentially curable cancers [3].

In 2006, the Integrated Cancer Prevention Center was established in the Tel Aviv Sourasky Medical Center. The main goals are the prevention and early detection of colorectal, lung, breast, skin, prostate, ovary, uterine, cervical, testicular, oral cavity and thyroid cancers. The Center also educates and promotes healthier lifestyles, such as a healthy diet, regular physical activity, and programs for avoiding tobacco and excessive alcohol use. In addition to the usual screening modalities, the Center is currently studying the association between polymorphisms in the *APC* and *CD24* genes and cancer risk. We used these polymorphisms to evaluate the general concept regarding the role of polymorphisms in screening asymptomatic population for cancer. CD24, a short mucin-like protein that until recently was regarded solely as a cell marker on hematopoietic cell lineage, was recently shown to be highly expressed in tissue samples from a large variety of solid and hematologic tumors. A certain polymorphism (Val/Val) in the protein was correlated with higher risk for cancer [4-7]. Similarly, variants of the *APC* gene (I1307K, E1317Q) were associated with an increased risk of colorectal cancer [8,9].

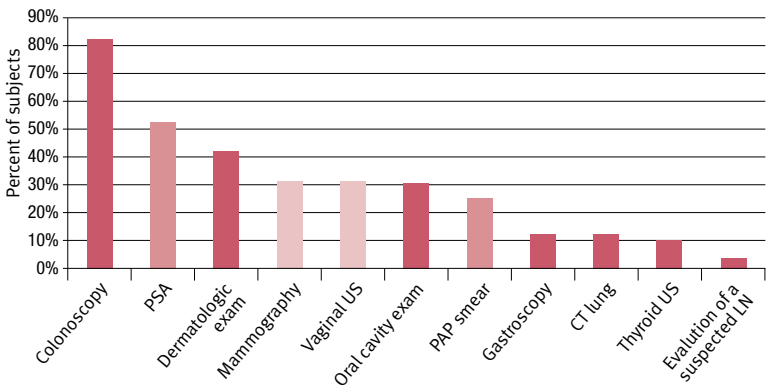
Table 1. Screening and surveillance recommendations

Cancer type	Age at initiation (yrs)	Surveillance	Physician
Breast	25	Breast self-exam monthly	
	25	Annual exam	Experienced surgeon
	40 (or earlier based on earliest age of onset in family)	Mammography every other year	
	50 (or earlier based on earliest age of onset in family)	Annual mammogram	
Colon	50	Colonoscopy every 5 years	Experienced gastroenterologist
Ovaries	25	Annual transvaginal ultrasound	Experienced gynecologist
Uterus and cervix	25	Annual pelvic exam with transvaginal ultrasound and Pap smear	Experienced gynecologist
Skin	25	Annual exam	Experienced plastic surgeon/dermatologist
Oral cavity	25	Annual exam	Dental surgeon
Prostate	40	PSA with rectal examination	Experienced internist and experienced urologist when indicated
Testicles	25	Annual exam	Experienced Internist and experienced urologist when indicated
Thyroid gland	25	Annual exam	Experienced internist and thyroid ultrasound when indicated
Lung*	40	Annual low dose CT for heavy smokers with › 2 decades of tobacco use	

*A low dose CT is performed only after discussing its value with the patients. Not all authorities recommend screening for lung cancer.

PSA = prostate-specific antigen

Figure 1. Distribution of non-routine tests that were administered when indicated. PSA = prostate-specific antigen, US = ultrasound, CT = computed tomography, LN = lymph node.



We evaluated the yield of an integrated cancer prevention center dedicated to cancer prevention and early detection and present our findings in this report.

SUBJECTS AND METHODS

We carried out a prospective analysis of the first 300 consecutive asymptomatic adults who attended our institutional Integrated Cancer Prevention Center between January 2006 and January 2008. The subjects were informed of the screening mainly through the media (TV, radio, newspapers). The study was approved by the Tel Aviv Sourasky Medical Center Helsinki Committee.

DATA COLLECTION

All subjects completed a detailed epidemiological questionnaire that included items on nutrition, physical activity, smoking, alcohol intake, use of medications, personal and family history of cancer, and other risk factors for malignancy. The subjects were interviewed and underwent a comprehensive physical examination by a single experienced physician (N.A.) who tailored the screening plan according to the individual's risk factors and findings in the physical examination [Table 1 and Figure 1]. All subjects had a thorough dermatologic examination; all men had a testicular exam; and all women had a transvaginal ultrasound, Pap smear [10] and manual breast examination. Complete blood count and inflammatory markers (C-reactive protein and fibrinogen) were evaluated in all participants. The screening tests consisted of prostate-specific antigen for all men above the age of 40 [11], colonoscopy for all men older than 40 and all women older than 50 [12], mammography for all women over age 40 [1,13], and low dose chest computed tomography in a few heavy smokers (more than 40 pack years) – after a thorough review of the pros and cons of such screening [14,15]. Other blood and diagnostic tests, such as gastroscopy and CT enterography, were performed as needed based on symptoms, family history, and individual risk factors. Participants who signed an informed consent underwent genetic counseling and were tested for genetic polymorphisms in the *CD24* and *APC* genes. Neoplastic lesions were classified according to the site of lesion and whether it was benign (localized tumor that does not invade the surrounding tissue or metastasize to a distal site) or malignant.

To verify the information on cancer morbidity and mortality in the study population, the data were compared with the Israeli Cancer Registry in the Ministry of Health (data not published).

GENETIC TESTS

DNA was extracted from peripheral blood mononuclear cells, as previously described [16]. DNA samples were examined

for their *CD24* polymorphism using restriction fragment length polymorphism analysis. DNA fragments bearing the single nucleotide polymorphism site were amplified by a PCR reaction. The predicted *CD24* PCR fragment was 522 bp long. The T-→C nucleotide change yielded a *BstXI* restriction enzyme site at nucleotide 327, which allowed us to differentiate between the two different CD24 alleles. Similarly, the *APC* variants were identified using specific primers as previously described [16].

STATISTICAL ANALYSIS

Pair-wise association between risk factors (gender, age, smoking, physical activity, personal and family history, polymorphisms, CRP level, etc.) and outcomes (findings of benign or malignant lesions) was examined by the $\chi 2$ test and presented as odds ratio with 95% confidence intervals. The analysis was performed twice, first for the entire cohort and second for the subjects without any known personal or family history of cancer. The SPSS for Windows software, version 14.0 (Chicago, IL, USA) was used for the analysis.

RESULTS

This pilot study comprised 300 consecutive asymptomatic subjects, whose mean age was 52 years (range 25–77), and 63.5% of them were males. There was a family history of cancer in 126 subjects (42%). Of note, more than two-thirds of the subjects were overweight (average body mass index 27.1 ± 13.4%), nearly half of them had a smoking history (mean 22.2 ± 44.3 pack years), and most of them (160/299) did not exercise regularly.

The two main reasons for referral of these asymptomatic individuals to the Center were health-consciousness (54%) or having a family member or friend with a malignant disease (37%). Each subject underwent regular screening tests and then additional evaluations according to his/her personal risk profile and the findings on physical examination. The frequencies of administering the various tests are shown in Figure 1. Overall, the incidence of neoplasia was 8.3%; a malignancy was detected in 10 subjects (3.3%) and benign lesions in 15 (5%). The most prevalent lesions (malignant and benign) were in the gastrointestinal tract (11/25, 44%), followed by skin (6/25, 24%), urogenital tract (6/25, 24%) and breast (2/25, 8%) [Table 2].

Data on the yield of the different screening tests are shown in Table 3. Skin and gastrointestinal lesions were most prevalent, while thyroid and oral cavity lesions were least prevalent. The results of inflammatory markers, such as complete blood count and fibrinogen, were not differentiated between subjects with or without malignancy (data not shown), but

PCR = polymerase chain reaction

Table 2. Relative frequency of benign and malignant lesions according to their anatomic location

Location	No. of benign lesions (%)	No. of malignant lesions (%)
Gastrointestinal *	7 (47%)	4 (40%)
Skin**	4 (27%)	2 (20%)
Gynecological ***	3 (20%)	1 (10%)
Breast ****	1 (6%)	1 (10%)
Prostate	–	2 (20%)
Total	15 (100%)	10 (100%)

* All benign lesions were neoplastic polyps of colon. All malignant lesions were adenocarcinoma of the colon.

** All benign lesions were basal cell carcinomas. All malignant lesions were squamous cell carcinomas.

*** All benign lesions were cervical intraepithelial neoplasias. The malignant lesion was ovarian cancer.

**** The benign lesion was a fibroma, the malignant lesion was ductal adenocarcinoma.

Table 3. Yield of the different tests in the study population

	Neoplastic lesions: positive (No.)/tested (total) (%)	
Test	Entire study population	Asymptomatic, average-risk subjects
Colonoscopy	11/248 (4.4%)	6/137 (4.4%)
Prostate-specific antigen	2/156 (1.3%)	1/87 (1.1%)
Dermatologic exam	6/127 (4.7%)	2/70 (2.9%)
Mammography	2/91 (2.2%)	1/44 (2.3%)
Vaginal ultrasound	4/94 (4.3%)	3/48 (6.3%)
Oral cavity	0/90 (0%)	0/51 (0%)
Pap smear	2/76 (2.6%)	1/40 (2.5%)
Gastroscopy	1/36 (2.7%)	1/13 (7.6%)
Low dose chest CT	1/36 (3%)	0/17 (0%)

CRP proved to be valuable since 17% of the subjects with a CRP level > 5 mg/L had a malignant lesion compared to 1% of subjects with normal CRP levels ($P = 0.01$).

AGE AS A RISK FACTOR FOR NEOPLASIA

As expected, being over 50 years old was significantly ($P = 0.01$) associated with increased prevalence of neoplasia. In our cohort, 18 subjects (13.2%) who were > 50 years old had a neoplastic lesion (both malignant and benign) and 9 (6.6%) had cancer, compared to 7 (5%) and 1 (0.7%) among subjects who were less than 50 years old, respectively ($P = 0.03$; OR 2.6, 95% CI 1.1–6.4, and OR 9, 95% CI 1.1–71). The evaluation of age as a risk factor in the asymptomatic average-risk subjects (no symptoms and no family history of cancer) revealed similar results.

CRP = C-reactive protein

Consistent with current knowledge, high levels of body fat (BMI), increased alcohol and cigarette consumption and reduced physical activity were correlated with a higher prevalence of malignant lesions (data not shown), although the correlation did not reach a level of significance.

GENETIC POLYMORPHISMS AND THE RISK FOR CANCER

The valine/valine polymorphism in the *CD24* gene was present in 7% of the cohort (n=21) and alanine/valine in 36% (n=107). *APC* I1307K and *APC* E1317Q polymorphisms were present in 6% (n=17) and 1% (n=2) of the subjects, respectively. Among the patients who were heterozygotes for *CD24* polymorphism, 4.7% (5/107) had a malignant lesion and 6.5% (7/107) a benign lesion. Most of the lesions were in the gastrointestinal, skin and gynecological systems. Among the homozygotes for the polymorphism, 10% (2/21) had a malignant lesion (both patients had prostate cancer) and 5% (1/21) had a benign lesion. Interestingly, in the subjects with the *APC* I1307K polymorphism, 18% (3/17) had malignant and not benign lesions ($P = 0.02$): their lesions involved the gastrointestinal tract, skin and prostate. In subjects with 0, 1 or 2 genetic polymorphisms, the risk for a neoplastic lesion was 5.6%, 11.1% and 23.1%, respectively ($P = 0.05$). The OR for neoplastic lesions in subjects with one or two polymorphisms compared to subjects with no polymorphisms was 2.1 and 5.1, respectively (95% CI 0.9–5.3 and 1.1–22, respectively). None of the subjects had all three polymorphisms. The risk for malignancy was 2.2%, 3.7% and 23.1% among subjects with zero, one and two polymorphisms, respectively ($P = 0.01$). The OR for malignancy was 1.7 and 14 in patients with one and two polymorphisms, respectively (95% CI 0.4–7.4 and 2.5–78, respectively). The most prevalent pair of polymorphisms was *CD24* heterozygosity and *APC* I1307K (10/13, 77%). All three cases of malignancy in patients with two polymorphisms had this combination (30%).

DISCUSSION

There is little controversy about the potential importance of preventive measures in terms of lifestyle choices and early detection of cancer in reducing morbidity and mortality from cancer. In this pilot study, we report our initial experience with the first 300 consecutive subjects who were evaluated in our institution's Integrated Cancer Prevention Center. This is the first report describing simultaneous screening and preventive interventions in an asymptomatic population during one session (with the exception of colonoscopy). Insofar as the subjects were self-referrals who were aware of the need for early detection of cancer, our cohort can be considered a health-conscious population. As such, we were surprised to discover that they do not all observe healthy lifestyles. Most of them did not exercise regularly, and more than half of them smoked tobacco and were above the desired BMI.

As might be expected, a significant number of benign and malignant lesions (5% and 3.3%, respectively) were detected among these asymptomatic screened subjects. These figures are much higher than the prevalence of cancer known in the general Israeli population, both for all sites and per site (data not shown, taken from the Israel Cancer Registry 2006 and the Israel Cancer Association). All pre-malignant lesions were removed uneventfully and all the cancer cases were diagnosed in an early stage with recovery following curative surgery.

Being older than 50 years proved to be a significant factor for determining the relevance of screening (OR 9 for malignancy compared to younger subjects). Most of the lesions were predictably detected in the gastrointestinal tract and the skin (two of the most common cancer sites in the Israeli population). Only one benign lung lesion was identified. Although lung cancer is the number one cause of cancer mortality worldwide [14], the prevalence is much lower in Israel and screening for lung cancer is therefore not carried out for the general population.

The more interesting findings of the current study are the importance of performing genetic polymorphisms in the *APC* and *CD24* genes. The odds ratio for subjects with one and two polymorphisms to develop malignancy was 1.7 and 14, respectively. Although these are negligible among SNPs, the association of the number of SNPs and the OR for cancer is promising but obviously needs verification in larger screening subjects. Clearly, more studies are needed to elucidate this genotyping-phenotyping association between SNPs and the risk for cancer.

It should be noted that a significant percent of our study population was not aware of being at high risk for cancer and hence of the need to undergo screening and surveillance. Indeed, a positive family history had an OR of 3 in predicting cancer occurrence.

The current study has three major limitations. First, the small number of subjects precluded certain subgroup analysis. Nevertheless, we consider it important to report on this unique multidisciplinary screening facility. Second, the ultimate impact of prevention and early detection on the incidence and prevalence of cancer, and mortality in particular, is beyond the scope of the present study. Another caveat of our study is that although we were addressing an average-risk population, 40% of the examined subjects had a positive family history of cancer, indicating a somewhat higher than expected prevalence of cancer risk in that population.

In conclusion, we present our initial report on a unique

BMI = body mass index

SNP = single nucleotide polymorphism

facility devoted to cancer prevention in apparently healthy adults. The ability to detect occult cancer, the importance of age as a risk factor, and the increased risk associated with certain genetic polymorphisms are impressive and warrant further studies on the potential benefits of this manner of prevention and early detection to society as a whole.

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Correspondence:
Dr. N. Arber
Integrated Cancer Prevention Center, Tel Aviv Medical Center, 6 Weizmann St., Tel Aviv 54239, Israel
Phone: (972-3) 697-4968
Fax: (972-3) 695-0339
email: narber@post.tau.ac.il

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