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Original article

Screening programs for colorectal cancer in Greece: Results of two pilot studies conducted in March 2008 and 2009

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SUMMARY

Background: Detection of occult blood in stools is an established method for the early detection of colorectal cancer in asymptomatic individuals of average risk. The aim of this study was to present the results derived from the application of the test in a cohort of Greek population of average risk. Subjects and Methods: We conducted two pilot studies in March 2008 and 2009 respectively. The first was conducted only in the greater area of Athens while the second one included two more major cities in the North and South part of the country (Salonika and Iraklion, Crete). In both campaigns all residents, aged between 55 and 72 years were asked through relevant television spots, articles in newspapers, radio spots and press conferences to participate in both studies (March 2008 and March 2009), by submitting a stool sample in the nearest "Biomedicine" Laboratory. For the detection of haemoglobin in stools LINEAR immunochemical FOBT was applied. This test is a qualitative, lateral flow immunoassay for the detection of human hemoglobin in stools. In order to include in the statistical analysis more than 90% of all examined individuals, we divided the number of subjects participating in the 2009 trial into three groups aged 55-60, 61-66, and 67-72 years. Moreover, in order to be able to calculate the odds ratios, these groups were transformed from numerical to nominal ones. Statistical analysis was performed using Pearson chi square test. Results: 1st trial, March 2008: The total number of individuals examined was 4,010. The rate of positivity was 9.83% (394 out of 4,010 individuals examined). Among the positive samples 30.2% corresponded to subjects aged 55-60 years, 35.3% to subjects aged 61-65 years and 34.5% to subjects aged 65-70 years. 2nd trial, March 2009: The total number of individuals tested was 7,079 with 3,131(44.2%) being men and 3948(55.8%) being women. The participation rate was: Athens 5,037 (71.1%), Salonika 1,407 (19.9%) and Iraklion 635 subjects (9.0%). The positivity rate was 11.1% (786 out of 7,079 subjects). The positivity rate among men (11.9%) (373/3,131) was higher compared to women (10.5%) (413/3,948) although this difference did not reach statistical significance (P=0.057). Mean age of the positive subjects was statistically significantly higher compared to negative ones (62.4 vs 61.9yrs, P=0.01). Significant differences existed between group 1 (55-60 years) vs group 3 (67-72 years). So, the probability of a positive test in the age of 67-72 was 1.36 times higher than at the age of 55-60 and the probability of a positive test in the age of 67-72 was 1.26 times higher than at the age of 61-66. Statistically significant difference in the positivity rate of the test between the three areas was noticed. So, residence was responsible for the variation in positive rate of FOBT by 6.9% (Eta statistics). Conclusion: The rate of positivity of iFOBT in Greece is in accordance with that reported in the relevant international literature and remains steady, at least during the years 2008 and 2009. However, it seems to be lower in areas adopting the so called Mediterranean diet (Iraklion, Crete). Taking into account the number of inhabitants of the country over the age of 55, we can assume that the compliance of the Greek population in colorectal cancer screening programs is relatively low. In the forthcoming years, screening programs in Greece must be adopted by the health authorities of the country in order

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to cover a larger part of the population. The experience derived from our studies could result in more successive and productive future programs.

Key Words: Colorectal cancer, screening, surveillance, fecal occult blood test, prevention

INTRODUCTION

Prevention of CRC could be divided into primary - including mainly environmental and dietetic modifications - and secondary through various screening programs. The goals of screening are to detect early asymptomatic CRC and polyps thus preventing cancer development through endoscopic polypectomy and promoting less-costly treatment.

The available methods include established modalities of screening such as fecal occult blood testing (FOBT), flexible sigmoidoscopy and colonoscopy, as well as newer methods such as virtual colonoscopy, fecal DNA, and capsule endoscopy.[1-3]

FOBT can reduce CRC mortality effectively. In a recently published Cochrane review which included four randomized controlled trials with 329,642 patients, FOBT reduced CRC mortality by 16 percent. Colorectal cancers were also detected earlier in the screening group.[4]

The aim of this study was to present the results obtained from the application of the test in a cohort of Greek population of average risk.

SUBJECTS AND METHODS

We conducted two pilot studies in March 2008 and 2009 respectively. The first one was conducted only in the greater area of Athens while the second included two more big cities in the north and south of the country. The studies were conducted with the collaboration of the non-governmental, non-profit organization «ΑΓΚΑΛΙΑΖΩ» and the Center for Health Services Research, Medical School, University of Athens. The pharmaceutical company Roche Hellas covered the cost of all activities related to advertising the project (newspapers, TV spots, press conferences etc), while the "Biomedicine" laboratories performed all iFOBTs.

In both campaigns all residents of the above mentioned regions, aged between 55 and 70 years were asked through relevant television spots, articles in newspapers, radio spots and press conferences to participate in the study. Specifically, they were asked to submit a stool sample to the nearest "Biomedicine" Laboratory.

For the detection of haemoglobin in the stool samples LINEAR iFOBT was applied. This test is a qualitative, lateral flow immunoassay for the detection of human occult blood in feces. The membrane is pre-coated with anti-hemoglobin antibody on the test line region of the test. During testing, the specimen reacts with the particle coated with anti-hemoglobin antibody. The mixture migrates upward on the membrane chromatographically by capillary action to react with anti-hemoglobin antibody on the membrane and generate a colored line. The presence of this colored line in the test line region indicates a positive result, while its absence indicates a negative one. LINEAR iFOBT is a rapid test to qualitatively detect low levels of fecal occult blood. It selectively detects fecal occult blood at 50 ng/mL or higher or 6 μg/g feces.

Patients were also asked to follow some guidelines such as; *"Specimen should not be collected during or within three days of a menstrual period.",* or *"Are you suffering from bleeding hemorrhoids?"* Moreover, subjects were asked to avoid alcohol consumption, aspirin and other medications at least 48 hours prior to testing. Dietary restrictions were not necessary as iFOBT detects only human hemoglobin.

STATISTICAL ANALYSIS

In order to include in the statistical analysis a percentage of more than 90% of all examined individuals, we decided to divide the number of subjects participating in 2009 trial into three groups aged 55-60, 61-66, and 67-72 years. Moreover, in order to be able to calculate the odds ratios, these groups were transformed from numerical to nominal ones.

Statistical analysis was performed by using Pearson chi square test.

RESULTS

A) 1st trial: March 2008

The total number of individuals examined was 4,010. The participation rate according to age was: 55–60 years: 38.5%, 60–65 years: 34.2% and 65-70 years: 27.4%. The participation rate according to sex was not evenly distributed. So, in the group of 55 to 60 women participated at a relatively higher rate (64%), compared to 57.7% in the group of 60 to 65 years of age. In the group of 65 to 70 years, men participated at a rate of 55.1%.

Concerning the rate of positivity it was found that the test was positive in 394 (9.83%), out of 4010 individuals examined. Among the positive samples 30.2% cor-

responded to subjects aged 55-60 years, 35.3% in subjects aged 61-65 years and 34.5% in subjects aged 65-70 years. Although the rate of positivity in the group of 55 to 60 years was higher among women compared to men (58.5% *vs* 41.5%), in the group of 60-65 the positivity rate was higher among men (52.2%). The rate was even higher among the men aged 65-70 compared to women (58.5% *vs* 41.5%).

B) 2nd trial: March 2009

The total number of individuals tested was 7,079 with 3,131(44.2%) being men and 3,948(55.8%) being women.

The participation rate in the three areas of the country was: Athens 5,037 (71.1%), Salonika 1,407 (19.9%) and Iraklion 635 subjects (9.0%).

The positivity rate in all individuals examined was 11.1% (786 out of 7,079 subjects). The positivity rate among men (11.9%) (373/3,131) was higher compared to women (10.5%) (413/3,948) although this difference did not reach statistical significance (P=0.057). The mean age of the positive subjects was statistically significantly higher compared to negative ones (62.4 vs 61.9 yr, P=0.01).

Table 1 shows the results of the comparison of positivity rate of FOBT between the three age groups. The results of Pearson Chi Square test indicated that there was a significant difference in positivity of the test across the age groups but did not discriminate between which groups this difference really exists. The results of Linear by Linear Association indicated that there was a significant trend for positive tests to increase with age. The Eta statistic indicates that only 3.5% of the variance of positivity could be explained by age range.

Further analysis indicates that significant differences existed between group 1 (55-60 years) vs group 3 (67-72 years) (Table 2). Actually, the results showed that the probability of a positive test at the age of 67-72 is 1.36 times higher than at the age of 55-60.

Table 3 shows the results of the comparisons between the age group 61-66 and 67-72 years. As the table indicates there were significant differences between the two groups. Actually the probability of a positive test in the age of 67-72 was 1.26 times higher than the age of 61-66.

Table 4 shows the positivity rate in the three areas of the country. As indicated in the table a statistically significant difference in the positivity rate between the three areas was noticed. It has been estimated that residence was responsible for the variation in positive rate of FOBT by 6.9% (Eta statistics).

The significant difference accounts for differences between Athens and Salonika and between Athens and Iraklion with a smaller odds ratio for residents of Iraklion (0.48) than Salonika (0.64) in respect to residents of Athens (Tables 5 and 6).

Concerning the distribution of positivity of the test in respect to age in the three areas of the country it was noticed that an increase in the positivity of FOBT with age in Athens but not in Salonika and Iraklion certainly exists. Addition-

Table 1. Comparisons between the three age groups (2009 trial).

Age group	Total	Negative	Positive
55-60 yrs	2,730	2,445 (89.9%)	275 (10.1%)
61-66 yrs	2,720	2,427 (89.2%)	293 (10.8%)
67-72 yrs	1,310	1,137 (86.8%)	173 (13.2%)
TOTAL	6,760	6,019 (89%)	741 (11.0%)

Pearson Chi-Square test = 0.011, Linear-by-Linear Association = 0.005, Eta statistic: 0.035

Table 2. Comparison between age groups 55-60 and 67-72 years (2009 trial)

Age group	Negative	Positive	Total
55-60	2,445 (89.9%)	275 (10.1%)	2,730 (100.0%)
67-72	1,137 (86.8%)	173 (13.2%)	1,310 (100.0%)
TOTAL	3,592 (88.9%)	448 (11.1%)	4,040 (100.0%)

Pearson Chi-Square test = 0.003, Odds Ratio = 1.358, 95% CI: 1.109-1.664

Table 3. Comparison between age groups 61-65 and 66-72 years (2009 trial)

Age group	Negative	Positive	Total
61-66	2,427 (89.2%)	293 (10.8%)	2,720 (100.0%)
67-72	1,137 (86.8%)	173 (13.2%)	1,310 (100.0%)
TOTAL	3,564 (88.4%)	466 (11.6%)	4,030 (100.0%)

Pearson Chi-Square test = 0.024, Odds Ratio = 1.260, 95% CI: 1.031 - 1.540.

Table 4. Comparison of the positivity rate in the three areas of the country.

Prefecture	Total number of individuals examined	Negative	Positive
Athens	5,037	4,409 (87.5%)	628(12.5%)
Salonika	1,407	1,290 (91.7%)	117 (8.3%)
Iraklion	635	594 (93.5%)	41 (6.5%)
TOTAL	7,079	6,293 (88.9%)	786 (11.1%)

Pearson Chi-Square test = 0.0001, Linear-by-Linear Association = 0.0001 Eta statistic: 0.069

Table 5. Comparison of the positivity rate in Athens and Salonika.

Area	Total number of subjects	Negative	Positive
Athens	5,037	4,409 (87.5%)	628(12.5%)
Salonika	1,407	1,290 (91.7%)	117 (8.3%)

Pearson Chi-Square test = 0.0001, Odds ratio 0.64 (95% CI=0.518-0.783)

Table 6. Comparison of the positivity rate in Athens and Iraklion.

Area	Total number of subjects	Negative	Positive
Athens	5,037	4,409 (87.5%)	628(12.5%)
Iraklion	635	594 (93.5%)	41 (6.5%)

Pearson Chi-Square test = 0.0001,Odds ratio 0.48, 95% CI=0.349 - 0.672)

ally, only in the Athens area is there a significant difference in the positivity rate among the age groups (Table 7).

At every age group the FOBT positivity rates were significantly higher in Athens compared to Salonika or Iraklion respectively. No significant difference existed between Salonika and Iraklion in all age groups.

DISCUSSION

FOBT is an established screening method for CRC having the advantage of being a non-invasive test. The available modalities of FOBT include the guaiac unrehydrated and rehydrated test and the immunological (iFOBT) test. The guaiac FOBT (gFOBT) requires some restriction of red meat from the diet, whereas iFOBT does not. This is because gFOBT detects haemoglobin generally while iFOBT detects only human hemoglobin. The second great difference is that gFOBT requires three consecutive fecal samples while iFOBT only one.

We decided to use the immunochemical test in our effort to promote the campaign against CRC by inviting people of average risk between 55 and 70 years to participate in the study. Instead of sending the test by post we decided to invite people to submit a stool specimen to the nearest, to their residence "Biomedicine" laboratory thus giving us also the opportunity to obtain demographic details and to explain the nature of the study and the expected benefits for the participants.

The results showed that the overall positivity rate fluctuates between 10 (2008) and 11% (2009 trial), being slightly higher in males with a tendency to increase with age. So, the probability of a positive test at the age of 67-72 was 1.36 times higher than at the age of 55-60 and the probability of a positive test at the age of 67-72 was 1.26 times higher than at the age of 61-66. Finally, the mean age of the positive subjects was statistically significantly higher compared to negative ones.

In all regions the participation of individuals aged between 66 and 72 years was lower compared to individuals aged 55 to 60 and 61 to 66 (Salonika 26.4%, Athens 24.5% and Iraklion 22% respectively). The low rate of participation in the older people can not be easily explained. It seems that either the message did not properly reach the target population, or the people did not understand the actual risk of CRC development at this age.

Another interesting finding of this study was the low positivity rate in the Iraklion prefecture in the south of Greece. Actually the rate of positivity was significantly lower at all ages compared to Athens and Salonika. Another interesting finding was the fact that the participation rate of the local population was quite higher in comparison with Salonika and Athens. We have no obvious explanation for these epidemiological peculiarities, although the traditional Mediterranean diet adopted for centuries in Crete, could explain, at least in part, the low rate of iFOBT positivity. It is well known that the incidence of CRC in this particular area is lower compared to other regions of either Greece or Europe. It was encouraging that the participation of the local population in the screening program was enthusiastic despite the fact that such a screening program for CRC was applied for the first time in Crete.

Findings quite similar to ours were described in a recently published study from Canada.[5] The sample included 16,747 residents of Newfoundland, Ontario, Saskatch-

Table 7. Distribution of FOBT results in the three areas of the country according to age.

	Athens (*)		Salonika (**)		Iraklion (***)	
Age	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**	**Positive**
55-60	1,710 (88.7%)	218 (11.3%)	490 (92.3%)	41 (7.7%)	255 (94.1%)	16 (5.9%)
60-61	1,771 (87.9%)	243 (12.1%)	429 (93.1%)	32 (6.9%)	228 (92.7%)	18 (7.3%)
62-72	788 (84.9%)	140 (15.1%)	246 (89.8%)	28 (10.2%)	103 (94.5%)	6 (5.5%)

Pearson chi square: (*)P=0.014, (**)P=0.271, (***)P=0.783

ewan and British Columbia. Overall, the FOBT screening rate was 7.7%. iFOBT screening rates were higher in older and male respondents; The authors concluded that national survey data suggest CRC screening in Canada is low and that younger persons were least likely to report CRC screening. In another study performed in Uruguay a quite high rate, very similar to the positivity rate found in our study was noticed. In fact the rate of iFOBT positivity among 11,734 individuals of average risk was 11.1% (1170 out of 11,734).[6]

Concerning sensitivity and specificity it seems that the iFOBT CRC, demonstrates a significantly higher sensitivity and specificity compared to gFOBT. It also represents the most cost-effective approach for non-invasive CRC screening. In a recently published statement of the US Preventive Services Task Force[7] it was reported that iFOBTs had higher sensitivity for CRC (61% to 91%)[8-17] than was reported for nonrehydrated Hemoccult II (25% to 38%) in both, a systematic review[18] and in a study of fecal immunochemical testing that also evaluated Hemoccult II.[10] Estimated specificity varied across fecal immunochemical tests (91% to 98%), and, in most studies, specificity appears lower than the reported specificity of nonrehydrated Hemoccult II (98% to 99%).[10] Sensitivity for advanced neoplasia or large adenomas was less commonly reported but ranged from 27% to 67% for fecal immunochemical tests.[10,11,14-16] The sensitivity of nonrehydrated Hemoccult II for large adenomas has been estimated at 16% to 31%.[18] The single study directly comparing HemeSelect and nonrehydrated Hemoccult II reported twice the sensitivity for polyps 10mm or greater for HemeSelect (67% vs. 31%).[10] Hemoccult SENSA had higher sensitivity for colorectal cancer (64% to 80%) than would be expected for Hemoccult II but lower specificity (87% to 90%).[8,9] In direct comparisons, Hemoccult SENSA was less sensitive for colorectal cancer (64%) than was FlexSure OBT/Hemoccult ICT (82%) but more sensitive for large adenomas (41% vs. 30%). Hemoccult SENSA was more sensitive for colorectal cancer (79%) than HemeSelect (69%) but had similar sensitivity for large adenomas (69% vs. 67%, respectively). Hemoccult SENSA was less specific for colorectal cancer and for adenomas compared with both fecal immunochemical tests.[9]

Concerning the situation in the European Union, CRC screening is not standard and there are great variations between countries in organization, intervals, ages and test methods. Most programmes and projects do not exceed much over 50% in participation, and serial participation is worse. There are European countries with CRC screening, which can be distinguished as formal, opportunistic, pilot and inactive screening programs. There is much variation in screening methodology, including delivery, age, intervals, tests and funders. Delivery may be via mailed tests, picked up from primary care, or via endoscopy. The age of initiation ranges from 50 to 60 years, while completion ranges from 69 to indeterminate. Most European FOBT screening programs, have found 0.6-0.9 CRC per 1,000 screening invitations. Screening will also detect more carcinomas in earlier rather than later stages. Various screening programs have found that 24-55% of CRC are at Stage A, 17-24% at Stage B and 20-30% at Stage C/D, and 19% polyp adenomas.

In conclusion, the rate of positivity of iFOBT in Greece is in accordance with that reported in the relevant international literature and remains steady, at least during the years 2008 and 2009.

Taking into account the number of inhabitants of the country over the age of 55 we can assume that the compliance of the population is generally low.

In the forthcoming years, screening programs in Greece must be adopted by the health authorities of the country in order to be applied to larger parts of the population.

The experience derived from our studies could result in more successive and productive future programs.

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