Fourteen-year retrospective study on fecal occult blood test in a private laboratory in Brazil

Pesquisa de sangue oculto nas fezes em um laboratório privado: Um estudo retrospectivo de 14 anos

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RESUMO
Introdução: O câncer colorretal (CCR) é a terceira neoplasia mais comum no mundo e apresenta altas taxas de mortalidade. A pesquisa de sangue oculto nas fezes (PSOF) é um método de rastreamento simples, não invasivo e validado para rastreamento do CCR. Objetivo: Avaliar os diferentes métodos de PSOF, suas taxas de positividade ao longo dos anos e aderência individual ao exame. Metodologia: Trata-se de estudo transversal retrospectivo que avaliou todos os registros de PSOF realizadas em um laboratório de 2005 a 2019. Os pacientes foram agrupados por faixa etária e sexo e a taxa de positividade foi analisada. A PSOF foi feita em duas etapas até 2015: triagem com guáíaco e, se positivo, confirmava-se o resultado com imunoquímico. Desde 2016, todas as PSOF foram realizadas com o imunoquímico. A amostra final foi de 316,287 exames de 136,735 pacientes. Resultados: 68% dos exames foram realizados em mulheres. Homens tiveram mais resultados positivos (p < 0.001). Houve diferença significativa nas taxas de positividade até 2015 e de 2016 a 2019, quando o único método realizado foi o imunoquímico (1.3% vs. 10.0%; p < 0.001). A proporção de resultados positivos aumentou significativamente com a realização de mais de uma amostra e de mais exames.
ao longo dos anos (p < 0.001). Conclusão: Esse estudo mostra a importância de campanhas de rastreamento de CCR direcionadas aos homens. O método imunoquímico deve ser empregado como padrão devido a sua maior sensibilidade. Indivíduos que realizaram mais amostras e mais exames têm chance aumentada de rastreamento positivo.

**Palavras-chave:** Neoplasias Colorretais; Programas de Rastreamento; Sangue Oculto; Guaiáco.

**ABSTRACT**

**Background:** Colorectal cancer (CRC) is the third most common neoplasia worldwide and has high mortality rates. The fecal occult blood test (FOBT) is a simple, noninvasive and validated screening method in CRC. **Objective:** To assess the changes in FOBT’s methods, positivity rates and individual adherence to the exam. **Methods:** This is a retrospective cross-sectional study that assesses all records of FOBT performed in a laboratory between 2005 and 2019. Patients were grouped by age range and gender and the FOBT positivity rate was analyzed within these groups. The laboratory performed FOBT in two stages until 2015: screening with gFOBT and, if positive, a confirmation with monoclonal was made. Since 2016, all FOBTs in this laboratory have been performed with the FIT method. The final sample had 316,287 exams from 136,735 patients. **Results:** 68% of the tests were performed in women. Men had more positive results (p < 0.001). There was significant difference between positive rates until 2015 and from 2016 to 2019, when all FOBTs started to be performed with fecal immunochemical test (FIT) (1.3% vs. 10.0%; p < 0.001). The proportion of positive results significantly increased with the performance of more than one sample and more exams over the years (p < 0.001). **Conclusion:** This study shows the importance of CRC screening campaigns targeting especially men. FIT should be used as the standard FOBT method, due to its higher sensibility. Individuals that perform more samples and exams along the years are more likely to have a positive screening.

**Keywords:** Colorectal Neoplasms; Early Detection of Cancer; Fecal Occult Blood; Guaiac-Based Test.

**1 INTRODUCTION**

Colorectal cancer (CRC) is the third most common neoplasia worldwide, representing the second cause of cancer-related death in 2020.\(^1\)\(^,\)\(^2\) Screening programs are able to reduce not only its incidence but also the mortality rate.\(^1\)

Screening methods for CRC include fecal occult blood test (FOBT), multi-targeted stool DNA test (mt-sDNA), sigmoidoscopy and colonoscopy. The FOBT is a simple, noninvasive and validated test used to decide whether the patient should be further investigated with a colonoscopy.\(^1\) A Cochrane systematic review has shown that FOBT results in a relative reduction in CRC mortality of 16%.\(^3\)

There are two major stool blood-based tests available: Fecal immunochemical test (FIT) and Guaiac-based fecal occult blood test (gFOBT). The FIT uses monoclonal
antibodies to detect blood in the stool, whereas gFOBT detects hemoglobin through a chemical reaction. \(^{(1)}\) FIT usually requires one or two samples of stool, while gFOBT requires three consecutive samples. Several studies comparing both methods showed that FIT has higher detection rate for CRC and advanced adenomas due to its higher sensitivity and greater individual participation. \(^{(1,4)}\)

The aim of this study is to provide a fourteen-year retrospective data on FOBT results at a private clinical laboratory in order to assess the changes in methods (gFOBT to FIT), positivity rates, individual adherence and discuss the test’s misuse.

2 METHODS

This is a retrospective cross-sectional study that assesses all records of fecal occult blood tests performed in a private clinical laboratory in Brazil. This study was approved by the local ethics committee (Faculdade de Ciências Médicas de Minas Gerais FCMMG – approval number 26942919.1.0000.5134). Due to the retrospective nature of the study, explicit consent was waived by the ethics committee. Researchers did not have access to information that breaks confidentiality. The inclusion criteria was all the patients that performed FOBT in the laboratory between May 16, 2005 and December 31, 2019, which corresponded to all records of FOBT available in the laboratory’s data base until the moment of the research. The exclusion criteria were patients without identification of sex and age and exams with undefined results.

The American Cancer Society recommends screening in individuals between 45 and 75 years old. From 76 to 85, the decision should be weighted, whereas individuals over 85 should not be screened. \(^{(5)}\) Therefore, patients were grouped in three age ranges: under 45 years old, between 45 and 75 and over 75 years old. To discuss the test’s possible misuse, we considered that individuals under 45 and over 85 years old were outside screening age range. People at increased or high risk for colorectal cancer might need to be screened before 45 years old (e.g.: family history of CRC). \(^{(5)}\) Due to the retrospective nature of the study, it was not possible to assess if all individuals under 45 years old were at increased or high risk for CRC.

The laboratory performed FOBT in two stages until 2015: screening with gFOBT and, if positive, a confirmation with monoclonal was made. Since 2016, all FOBTs in this laboratory have been performed with the FIT method. Unfortunately, due to laboratory data processing, we were unable to assess patients who had a positive gFOBT but presented a negative FIT, thus having a negative final result.
The total sample had 316,287 test results from 136,735 patients. Of the total of exams, in 249,460 (91.4%) one sample was ordered, in 3,674 (1.3%) two samples, in 19,817 (7.3%) three samples and in 7 (0.003%) four samples were ordered (Figure 1). The latter were excluded due to the small number of patients. For multiple-sample exams, the patient was advised to collect samples from separate bowel movements.

Patients who brought two or more samples were considered to have positive results if any of the samples were positive. Exams with no results due to missing samples were used to evaluate individual adherence but were excluded to assess the prevalence of positive exams (resulting in a sample of 270,992 exams of 135,769 patients).

Categorical variables were presented as absolute and relative frequencies and numerical variables as mean ± standard deviation. The comparison between two groups was performed with Mann-Whitney test and the association between categorical variables was made with Chi-square test. The level of significance was set at 5% and the data were analyzed using software R version 4.0.3.

3 RESULTS

Of the 270,992 exams, 184,348 (68%) were performed in women. The mean age of the patients was 58.1 ± 15.0 years; 0.8% were under 18 years old; 15.9% were under 45; 71% were between 45 and 75; 13.1% were over 75; and 2.5% were over 85 years old. The total of exams performed increased within time in all age ranges (Figure 2).
In general, men had more positive results than women (Figure 3). When stratified by gender and age, the difference was statistically significant in under 45 years old (4.2% vs. 3.6%; p < 0.001) and 45-75 years old (5.1% vs. 3.9%; p < 0.001), but not in the age range above 75 (7.0% vs. 6.6%; p = 0.235).

Patients over 75 years old had more positive results (p < 0.001) than the other age ranges, whereas patients between 45 and 75 years old had more positive results than
patients under 45 (p < 0.001). There was significant difference between positive rates until 2015 and from 2016 to 2019 (1.3% vs. 10.0%; p < 0.001) in all age ranges. The subgroup analysis of 45-75 years old age range is shown on Table 1.

Table 1 – Distribution of results between exams performed until 2015 and from 2016 to 2019, for patients between 45 and 75 years old.

<table>
<thead>
<tr>
<th>Period</th>
<th>Result Positive</th>
<th>Negative</th>
<th>p-value(^Q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 to 2015</td>
<td>1,344 (1.1%)</td>
<td>120,159 (98.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2016 to 2019</td>
<td>6,831 (9.6%)</td>
<td>64,045 (90.4%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^Q\) Chi-Square Test

Of the total 249,460 one-sample exams, in 1,848 (0.7%) the patient did not bring the sample to the laboratory. Of the 3,674 two-sample exams, in 14 (0.4%) none of the samples were brought and in 20 (0.53%) one of the samples was brought. Of the 19,817 three-sample exams, in 104 (0.5%) none of the samples were brought, in 66 (0.3%) one of the samples was brought and in 83 (0.43%) two of the samples were brought.

There were discordant results in 5.4% of the two-sample exams. Of the three sample exams, 7.33% had discordant results. In 5.5% of the three-sample exams, only one of the samples was positive. Concordant positive results were only found in 2.1% of the two-sample method exams and in 1% of the three-sample method.

The proportion of positive results significantly increased (p < 0.001) with the performance of more than one sample (Table 2). The positivity was higher with three-sample exams (8.4%). The proportion of positive results also increased significantly (p < 0.001) and progressively with the performance of more exams over the years (Table 3).

Table 2 – Proportion of positive results according to the number of samples.

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>Number of exams</th>
<th>Result Positive</th>
<th>Negative</th>
<th>p-value(^Q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>247,698</td>
<td>0.278 (4.1%)</td>
<td>237,420 (95.9%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>More than 1</td>
<td>33,294</td>
<td>.938 (8.3%)</td>
<td>31,356 (91.7%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3,723</td>
<td>81 (7.5%)</td>
<td>3,442 (92.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9,564</td>
<td>1,650 (8.4%)</td>
<td>7,914 (91.6%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^Q\) Chi-Square Test

Table 3– Proportion of positive results according to the number of exams.

<table>
<thead>
<tr>
<th>Exams</th>
<th>Number of patients</th>
<th>Result</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>82,233</td>
<td>3,851 (4.7%)</td>
<td>78,382 (95.3%)</td>
</tr>
<tr>
<td>More than 1</td>
<td>3,536</td>
<td>5,855 (12.8%)</td>
<td>6,681 (87.2%)</td>
</tr>
<tr>
<td>1</td>
<td>82,233</td>
<td>3,851 (4.7%)</td>
<td>78,382 (95.3%)</td>
</tr>
<tr>
<td>2</td>
<td>23,809</td>
<td>2,133 (9.0%)</td>
<td>21,676 (91.0%)</td>
</tr>
<tr>
<td>3</td>
<td>1,654</td>
<td>1,427 (12.2%)</td>
<td>0,227 (87.8%)</td>
</tr>
<tr>
<td>4</td>
<td>6,487</td>
<td>649 (14.6%)</td>
<td>5,538 (85.4%)</td>
</tr>
<tr>
<td>5</td>
<td>1,100</td>
<td>689 (16.8%)</td>
<td>3,411 (83.2%)</td>
</tr>
<tr>
<td>More than 5</td>
<td>7,486</td>
<td>1,657 (22.1%)</td>
<td>5,829 (77.9%)</td>
</tr>
</tbody>
</table>

Q Chi-Square Test

4 DISCUSSION

In this fourteen-year retrospective analysis on FOBTs performed in a private clinical laboratory in Brazil, we have found that women had a greater participation than men, in agreement with numerous previous studies.\(^6\)\(^-\)\(^9\) This was probably because women tend to have more awareness of screening programs and are more likely to see doctors.\(^1\)\(^0\) CRC mortality rates are 25% higher in men,\(^1\) and this could be due to lack of adherence to screening.

The number of performed exams throughout the fourteen-years increased significantly. In 2019, there were 5 times more performed exams than in 2005. This demonstrates a rise in the interest in FOBT, especially when CRC started to be seen as one of the most preventable cancers in the world.\(^1\)\(^1\) This could be partially due to the expansion of the laboratory activities and prevention campaigns.

Individuals in the screening age interval, between 45 and 75 years old, corresponded to the majority of the exams performed (71%). Nevertheless, individuals outside the screening age range (under 45 and above 85) corresponded to 18.4% of the exams. No data regarding the exact indications for these exams were provided, but this shows a potential misuse of FOBT as a screening method. Peacock et al. showed that 68% of the FOBTs were made outside the screening age range and that 49 out of 85 patients with a positive result were not further investigated.\(^1\)\(^2\) Similar misuse of FOBT was found by Powell et al. and Van Rijn et al..\(^1\)\(^3\),\(^1\)\(^4\)

We identified that men had more positive results in the age ranges under 45 and between 45 and 75 years old. Several studies have found that FOBT positivity rates are higher in men,\(^8\)\(^-\)\(^1\)\(^0\) as well as CRC detection rates.\(^1\)\(^,\)\(^1\)\(^0\) CRC tends to be more proximal in women and FIT is less sensitive for proximal lesions, which could explain lower positivity in women.\(^1\) Since men typically have higher positivity and women have lower
CRC detection rates compared with men, the use of different cut-off levels between genders was assessed by Blom et al. This study found that cut-off rates of 40 and 80 μg/g for women and men, respectively, produced similar positivity; but further studies assessing gender specific cut-offs and CRC detection rates should be made.\(^{(15)}\)

Individuals over 75 years old had more positive results than the other age ranges. This could be due to the increasing incidence of lower gastrointestinal bleeding with age and the higher use of antiplatelets, anticoagulants and non-steroidal anti-inflammatory drugs among the elderly.\(^{(16)}\) Also, approximately 60% of CRC patients are > 70 years old and 43% are > 75 years.\(^{(17)}\)

There was a significant rise in the FOBT positivity rate in 2016. As previously stated, FOBT was performed in two stages until 2015: screening with gFOBT and, if positive, a confirmation with monoclonal was made. Since 2016, all FOBTs in this laboratory have been performed with FIT. Therefore, the increase in positivity rate could partially be explained by the higher sensitivity of FIT compared to gFOBT.\(^{(1,3,4)}\)

In a meta-analysis, sensitivity of FIT for one-time evaluation was 0.79 (95% CI 0.69-0.86) and specificity was 0.94 (95% CI 0.92-0.95).\(^{(18)}\) Another meta-analysis found that FIT is superior than gFOBT in the detection of CRC (RR 1.96, 95% CI 1.2-3.2) and advanced neoplasia (RR 2.28, 95% CI 1.68–3.10) with no loss of specificity.\(^{(19)}\) In a study that compared 3 samples FIT vs. 3 samples of gFOBT, it was also found that FIT has a higher detection rate of CRC and advanced adenomas despite lower compliance rate, indicating that FIT superiority is independent of individual participation.\(^{(20)}\) The American College of Gastroenterology replaced gFOBT for FIT as the preferred CRC detection test in 2008.\(^{(21)}\)

Many public and private laboratories in Brazil are still using gFOBT as the standard FOBT method, despite FIT’s known cost-effectiveness.\(^{(22)}\) We suggest that this should be carefully addressed, also taking colonoscopy capacity into account. A study made with FIT at a higher cut-off because of limited colonoscopy capacities, showed that FIT remains more effective and cost-effective than gFOBT.\(^{(23)}\)

The proportion of positive results significantly increased with the performance of more than one sample. It is noteworthy that increasing the number of samples could decrease adherence.\(^{(1)}\) The improvement in diagnostic-yield with collection of two or more samples of FIT remains controversial. Some studies suggest that performing two-sample FIT does not result in higher detection rate of CRC and that one-sample screening should be preferred.\(^{(24,25)}\) Other studies suggest that two samples have best detection rates
for CRC,\(^{(4,26)}\) whereas others state that three-sample FIT could be used as a screening method.\(^{(27)}\) However, other studies suggest that the diagnostic yield of collecting two samples can be achieved by performing one sample using a lower cut-off.\(^{(28)}\) The majority of screening programs are based on three-sample gFOBT and one-sample FIT. The US Multi-Society Task Force recommends one-sample FIT annually, stating that it has a low-quality evidence.\(^{(29)}\)

Discordant FOBT results were not neglectable. In a study by Muinuddin et al., the diagnostic yield for advanced adenoma varied directly with the number of positive samples (OR 3.0 [95% CI 1.2 to 7.3] for one positive FOBT and 6.5 [95% CI 2.8 to 15.0] for two or three positive FOBTs).\(^{(30)}\) In a large screening study, a quarter of patients with advanced neoplasia had discordant results.\(^{(31)}\) Therefore, our findings show that we could be possibly missing out the opportunity of diagnosing CRC by performing only one sample. However, further studies assessing multiple sample FOBT, compliance rate and diagnostic yield of CRC should be made.

In our study, patients that made more than one FOBT (one, two or three-sample method) were more likely to have positive results. Because of the large sample size, it was not possible to determine the time between the exams to the laboratory appropriately. However, our findings possibly suggest that individuals who have a higher adherence to CRC screening are more likely to have a positive screening. More studies should be made to assess if this results in a higher diagnostic yield.

Because it is a retrospective study with data from one of the clinical laboratories in a Brazilian city, we could be facing selection bias, undermining the external validity of the study. Also, we could be dealing with missing data.

**5 CONCLUSIONS**

Along these fourteen years, there was an important tendency of rise on FOBT demand. Women represented most of the population whereas male sex was responsible for the major rate of positive results. This shows the importance of CRC screening campaigns for the general population, targeting especially men due to the higher CRC mortality rates and significantly lower number of exams performed among this group. Our findings suggest a potential misuse of FOBT. Medical training programs should be carried out to advise doctors on the exam’s indications and limitations. We also advocate that more clinical laboratories consider adopting FIT as the standard FOBT method. New
prospective studies should be made to provide a standardized CRC screening guideline regarding number of FIT samples, time between screenings and gender specific cut-offs.

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DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest.
REFERENCES


