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European Journal of Cancer 37 (2001) 438–439

European Journal of Cancer

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Letters

Comments on: Recommendations on colorectal cancer (CRC) screening in the European Union. Advisory Committee on Cancer Prevention. *Eur J Cancer* 2000, **36**, 1473–1478

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Received 29 September 2000; accepted 10 October 2000

We read the Position Paper of the Advisory Committee on Cancer Prevention [1] with special interest in the section referring to colorectal cancer (CRC) screening and have the following comments.

The authors state that immunochemical faecal occult blood tests (FOBTs) are 'not recommended'. On this point, the document is unclear for it is not easy to understand to what extent the authors disregard this kind of test, nor do they indicate any other way to investigate this matter further.

All randomised trials demonstrating the efficacy of FOBT screening have been performed using unhydrated or rehydrated guaiac FOBT (Hemoccult II), a kind of test that can be affected by the peroxidase-like effect of non-human haemoglobins and several plant foods. For this reason, the positivity threshold has been put at a high level in order to minimise false-positive results due to diet. This explains the very low sensitivity of unhydrated guaiac FOBT. When rehydration is used, sensitivity increases with an important decrease in specificity.

For this reason, immunochemical FOBTs have been widely studied over the last two decades. Despite the chemical differences between immunochemical and guaiac FOBTs, they are both aimed at detecting bleeding, an indirect sign of the presence of cancer. Specificity for human haemoglobin makes immunochemical tests more efficient than guaiac tests as they are not influenced by diet. This allows a lowering of the positivity threshold with only minor effects on specificity due to non-neoplastic bleedings. Several technologies have been considered in this field such as enzyme-linked immunosorbent assays (ELISA), radial immuno-diffusion, reversed passive haemaglutination (RPHA) and latex agglutination. The test that has been most commonly compared with the Hemoccult II test has been RPHA.

RPHA, which was developed in Japan in the early 1980s, has been compared with Hemoccult II in several studies on patients with neoplasms or volunteers and in institution- or community-based screening programmes [2–5]. Whenever the two tests were compared, RPHA sensitivity for cancer was 9–85% higher than in the Hemoccult II test. Moreover, in several studies [3,5], RPHA sensitivity for adenomas >1 cm was higher compared with the Hemoccult II test. In a recent case–control study conducted in Japan comparing the efficacy of guaiac and immunochemical screening in reducing CRC mortality, a higher efficacy of immunochemical screening compared with Hemoccult II was evidenced [6].

In the majority of the above-mentioned reports [2–4], RPHA proved to be more specific than Hemoccult II. Nevertheless, in one study [5], Hemoccult II was more specific than RPHA (98.1% versus 95.2%). However, it should be considered that in this study, that recorded a positive rate (PR) of 2.5% for Hemoccult II, guaiac sensitivity was as low as 37.1% for cancer and 30.8% for >1 cm adenomas, whereas corresponding values for RPHA were 68.8 and 66.7%, respectively. Therefore, in this study RPHA showed the better balance between sensitivity and specificity.

Within our population-based screening programme, we have compared a 3-day rehydrated Hemoccult II and a 1-day RPHA testing [7]. Our results confirm the higher sensitivity of RPHA compared with guaiac testing despite the rehydration of the latter. In addition, specificity was also higher for the RPHA test compared with the rehydrated Hemoccult II test provided that a higher positivity threshold was adopted. As a result, RPHA screening (whatever the adopted threshold of

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PII: S0959-8049(00)00420-2

positivity) proved to be more cost-effective than rehydrated Hemoccult II as far as costs per subject detected with cancer or adenoma(s) >1 cm were concerned. The results of our cost analysis are consistent with the cost analysis conducted in Japan comparing RPHA and unhydrated Hemoccult II [2], and as in the Japanese screening programme, RPHA also proved to be more cost-effective than Hemoccult II.

The relative complexity of the RPHA development procedure may be simplified by means of the partial automation of the dispensing and reading phases using instruments provided by the manufacturer. This allows a shortening of the development time and a better standardisation of test results. To date in our screening programme in the Province of Florence, the PR ranges from approximately 4.5% at the first screening to 2.5% at the repeat screening.

Due to the above-mentioned considerations, RPHA has been used as a reference test in our CRC screening programme to date. However, more recently, we have been comparing the 1-day RPHA and the 1-day Latex agglutination test. The latter is a quantitative test allowing for the complete automation of the development procedure. Our results suggest that Latex performances are consistent with RPHA ones provided that a positivity threshold of 100 ng of haemoglobin/ml of sample solution is adopted [8]. For this reason, the Latex agglutination test has been introduced into our programme as an acceptable alternative to RPHA testing.

In our opinion, despite the existing evidence of the efficacy of guaiac testing in reducing CRC mortality, its inefficiency prevents a wide-scale adoption of CRC screening. The surplus of information now available on immunochemical tests is enough to encourage the use of immunochemical FOBTs in order to improve screening performances and cost-effectiveness.

Obviously, only tests with known quality standards and efficiency should be adopted, after a careful choice among the large variety of products available in the market, most of which do not fit the characteristics of screening tests.

As in any field of medicine, further studies should be encouraged to improve the quality of existing standards. What we do not agree with is to delay the possible use of tests that could improve the efficacy and the efficiency of FOBT-based CRC screening.

We strongly suggest the updating of existing recommendations by including immunochemical tests for CRC among currently available screening tools.

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