Editorial

What is the optimal interval for screening colonoscopy after diagnosis of a colorectal adenoma?

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Colorectal cancer (CRC) remains one of the most common causes of death in industrialized countries. The incidence rates vary among different populations, but are higher in males than females and increase with age. Obesity, diabetes, cigarette smoking, high alcohol consumption, eating red meat (particularly processed meat), and lack of physical activity are all recognised risk factors. Colorectal cancer is potentially amenable to secondary prevention by screening, because the detection and removal of an adenomatous polyp can prevent colorectal cancer from subsequently developing. In addition, when CRC is diagnosed while still localized (i.e., confined to the wall of the bowel), 5-year survival is likely to be extremely favourable in the region of 90%, but falls to 66% for stage II (i.e. disease with lymph node involvement). Hence, the principle of the benefit of colonsocopic screening is widely accepted. Yet the large numbers of colonoscopies required demands considerable resources, and existing guidelines tend not to provide estimates of resource implications.

Brenner *et al*.'s recent article in the *Journal of Clinical Oncology* (1) goes against European guidelines (2) and recommends that current colonoscopy surveillance intervals can be extended to a minimum of 5 years. In this population-based case-control study from Germany, the risk of CRC among participants with detection of at least one adenoma at a preceding colonoscopy was compared with participants without previous large-bowel endoscopy among 2,582 cases with CRC and 1,798 matched controls. Their recommendations are based on results which showed a significant risk reduction of colorectal cancer within 5 years for both men and women, younger and older participants, with and without high-risk polyps (defined as three or more polyps, at least one polyp ≥1 cm, at least one polyp with villous components), and those with and without polypectomy in the right colon.

This policy negates the need for a colonoscopy at 3 years for both low and high risk adenomas, which is recommended in recent European Guidelines (2) (Atkin 2012). This policy would therefore be welcomed by those who control the financial purse-strings as this reduction in the number of surveillance colonoscopies required would lead to financial savings and a likely reduction in adverse events risk by lowering the number of what might be considered 'unnecessary' endoscopies.

Up to 10% of adenomatous polyps will develop into invasive bowel cancer, with the result that the majority of adenomas removed may not ever progress to a colorectal cancer. However, when we analyse all the evidence, the conclusions are not that clear. In the study by Brenner (1), there was a significant CRC risk reduction by 60% in those who underwent a surveillance colonoscopy in less than 3 years and 50% risk reduction in the 3-5 surveillance interval after polypectomy for high-risk polyps. The risk reduction is therefore marginally higher in the shorter surveillance interval, and patients might choose any further chance in risk reduction, which would go against the recommendation for lengthening the surveillance interval for high-risk adenomas.

European age standardised incidence rates of CRC have increased by 27% between 1975-1977 and 2007-2009, with the most marked increase between the mid-1970s and late 1990s. This rise in incidence has been observed

despite widespread colonoscopy surveillance, suggesting that although we have reduced the incidence of adenoma in patients who have undergone colonoscopy, there remains a large number of the population who will not have had this endoscopic protection. This is shown in the present study where only 160 cancers arose in patients having undergone a colonoscopy and polypectomy compared with the overall large number of cancers [2,582].

This problem has been addressed by the introduction of colorectal cancer screening. Pilot studies showed reduction in CRC mortality by about 25% for either the use of faecal occult blood testing (3,4) or flexible sigmoidoscopy (5). In the UK, the cost of Bowel Cancer Screening is £77.3 million. The majority of patients who undergo colonoscopy following a positive initial test will have colorectal adenomas which will continue to increase the costs of screening. However, screening has the greatest potential to reduce the incidence of and mortality from colorectal cancer which is why Brenner *et al*. commented that 'colonoscopy resources could be used more efficiently by increasing the number of people who undergo a first colonoscopy and by extending surveillance intervals to 5 after colonoscopic detection and removal of polyps, even in the case of high-risk adenomas'.

Quality assurance is vitally important. The historical evidence suggests that following the initial colonoscopy where an adenoma is detected and removed, 30-50% of patients will have further adenomas detected within 3 years, but less than 1% will be found to have cancers. Some of these further adenomas and cancers have simply been missed at the baseline colonocopy. Clearly both education and training and the quality of the endoscopist in addition to the inherent characteristics of the polyps removed are crucial, since all will impact on the number of polyps/cancers found subsequently.

A population screening programme in the UK (The UK Flexible Sigmoidoscopy Screening Trial) reported long-lasting reduction of colorectal cancer (CRC) incidence and mortality by 33% and 43% respectively from CRC among those screened with a single flexible sigmoidoscopy (5). Only subjects with large distal polyps (≥10 mm) or with smaller advanced adenomas (<10 mm) were referred for total colonoscopy. In this study the few endoscopists were very highly trained surgeons with a very high throughput, and were in competition to remove the highest number of polyps.

However, there is a considerable variation in the recommendations for surveillance intervals after detection and removal of adenomas at colonoscopy (both within and between individual countries) (6). Once an adenoma has been removed, the optimal time interval to the next surveillance colonoscopy remains controversial. Adenomatous polyps are common with increasing age - particularly over 55, but the majority do not mature into adenocarcinoma. The evidence regarding both recurrence of the adenoma and the development of a cancer is patchy, empirical and mostly based on observations of adenoma recurrence. Adenomas have been defined as both high and low risk. One or two small adenomas with no high-grade dysplasia are considered low risk, and recommended to undergo colonoscopy every 5 years. In contrast, surveillance intervals of 3 years are often recommended for patients with high-risk adenomas - defined as a polyp ≥10 mm in size or high-grade dysplasia or those with polyps showing significant villous components. A family history of CRC or adenomas, and a history inflammatory bowel disease are also considered high risk, along with the recognised genetic syndromes predisposing to CRC.

Another observational study at a veterans hospital in California comprising 1,819 patients undergoing elective colonoscopy showed that 15% of individuals (who did not have Lynch Syndrome) had small nonpolypoid colorectal neoplasms seen with chromoendoscopy and these "flat" lesions were 10 times more likely to contain advanced dysplasia than polypoid lesions (7). More advanced histology may be present in 10% of small (5-10 mm) colorectal adenomas (8). Since carcinogenesis may be accelerated in Lynch Syndrome, improved detection of small lesions may be especially important in this patient population. Chromoendoscopy, performed by spraying dye on the colorectal mucosa during colonoscopy, has been reported to improve visualization of mucosal lesions.

British Society of Gastroenterology (BSG) guidelines are inherently logical but advocate screening for adenoma more frequently than screening for patients who have had cancer. Recent European guidelines for colonoscopic surveillance following adenoma removal (2) have been published by the European Commission. These new EU Guidelines provide 24 graded recommendations which aim to improve the quality and effectiveness of surveillance. These guidelines are based on the principle that "Patients can be divided into low, intermediate and high risk groups with respect to their risk of developing advanced adenomas and cancer based on findings at baseline colonoscopy" High risk (defined as >5 small adenomas or at least one >20 mm, intermediate risk as 3-4 adenomas and at least one 11-19 mm, and low risk as 1-2 adenomas and both small (<10 mm). The recommendation

for intermediate risk is a further colonoscopy within 3 years, and for high risk within 1 year (2). Clearly age, family history, the believed completeness of the procedure, all need to be known to assess the risk.

Advice offered on healthy lifestyle and how to avoid cancer at the time of cancer screening may also provide an unique opportunity to improve dietary behaviours as this may offer a "teachable moment" (9).

Conclusions

Ultimately, the decision on the optimal interval will be made by health organisations, because the definite increase in CRC incidence, the increase in colonoscopy numbers and the uptake of bowel cancer screening with recommendations to an increased age extension (as in the UK) may sway some to choose to intensify colonoscopic surveillance, rather than to increase the interval and concentrate resources saved on screening and educating the wider population.

Education, training and the quality assurance of endoscopy is the key to success. But large well conducted collaborative multicentre randomized trials are still needed with sufficient statistical power to clarify how to improve cancer prevention for individuals at high risk of developing CRC. For low risk adenomas adopting a healthy lifestyle is as likely to prevent bowel cancer as surveillance colonoscopy. The opportunity to utilise the teachable moment should not be missed.

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