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Aspirin Use and Survival After Diagnosis of Colorectal Cancer
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Background: Aspirin reduces risk of colorectal neoplasia in randomized trials and epidemiological studies and inhibits tumor growth and metastases in animal models. However, the influence of aspirin on survival after diagnosis of colorectal cancer is unknown. Methods: Among 1288 participants diagnosed with Stage I, II, or III colorectal cancer enrolled in two cohorts, we used Cox proportional hazards models to prospectively compare the effect of aspirin use before and after colorectal diagnosis on mortality. Results: Compared to non-users, participants who regularly used aspirin after colorectal cancer diagnosis experienced a multivariate hazard ratio (HR) for colorectal cancer-specific mortality of 0.72 (95% CI, 0.54-0.97) and overall mortality of 0.82 (95% CI, 0.67-1.00). Among 719 participants who did not use aspirin before diagnosis of colorectal cancer, aspirin use initiated after diagnosis was associated with a multivariate HR for colorectal cancer-specific mortality of 0.55 (95% CI, 0.34-0.89). Among 459 participants with colorectal cancers that were accessible for immunohistochemical assessment, the effect of aspirin differed significantly according to COX-2 expression (Pheterogeneity=0.04). Regular aspirin use after diagnosis was associated with a lower risk of colorectal-cancer specific mortality among those whose primary tumors overexpressed COX-2 (multivariate HR 0.39; 95% CI, 0.20-0.76) whereas aspirin use had no influence on those with primary tumor with weak or absent expression (multivariate HR 1.25; 95% CI, 0.37-4.22). Conclusions: Regular aspirin use after the diagnosis of colorectal cancer may reduce the risk of colorectal cancer-specific mortality, especially among individuals with tumors that overexpress COX-2.

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First Randomised Trial On the Risk of Colorectal Cancer After Flexible Sigmoidoscopy Screening
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Background: Despite the lack of evidence from randomised trials, many countries recommend endoscopic screening for colorectal cancer (CRC) for the general population. This is the first report from a randomised trial on the risk of CRC after flexible sigmoidoscopy (FS) screening. Methods: 55 736 individuals, aged 55-64 years, living in the city of Oslo or Telemark county, Norway, were randomised from the population registry to once-only FS screening with or without a single round of faecal occult blood testing (n=13 823), or no screening (n=41 913). The planned trial outcome measures were cumulative CRC incidence and mortality. We here present cumulative CRC incidence after 7 years and mortality hazard ratios (HR) after 6 years of follow-up. Results: In the intention-to-screen analyses (67% attendance rate), there was no difference in the 7-year cumulative CRC incidence between the screening and control groups (134.5 vs 131.9 cases per 100 000 person years). There was a trend towards reduced CRC mortality (HR=0.73, 95% CI 0.47-1.13, p=0.16). Screening attenders had a significantly reduced CRC mortality (HR=0.41, 95% CI 0.21-0.82, p=0.011) compared to controls, For rectosigmoidal CRC, the risk of dying from CRC was reduced by 76% (HR=0.24, 95% CI 0.08-0.76, p=0.016). CRC after screening occurred in 0.4% of screened individuals, compared to 0.8% of individuals in the control group. Conclusions: In an intention-to-treat analysis, a CRC incidence reducing effect of FS screening could not be demonstrated. However, a trend towards reduced CRC mortality in the screening group was seen. Individuals actually screened had significantly lower risk of dying from CRC compared to controls, indicating an effect of flexible sigmoidoscopy screening in those attending.

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Colorectal Cancer Despite Colonoscopy: Critical Is the Endoscopist, Not the Withdrawal Time
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Background: The rate of detection of advanced adenomas or colorectal cancer (**CC**) during colonoscopy (**C**) has a high correlation with endoscopist and the time taken to withdraw the endoscope. **Aim**: To investigate the impact of endoscopist and the withdrawal time on the development of CC not prevented by C (**CCdespiteC**) in patients undergoing screening or surveillance C at Mayo Clinic Rochester (**MCR**). **Methods**: A large dataset was created containing (1) patients who had undergone C at MCR between 1992 and 2002 (138,318 Cs in 98,960 patients), and (2) patients who had a tissue specimen diagnosis of CC between 1992 and 2004 (N=10,136). Withdrawal time was not recorded until 2002; therefore the average withdrawal time for each endoscopist was based on data from 2002 to 2006 and reflected Cs with indication as screening. A CCdespiteC was defined as a CC that was diagnosed 90 days to 3 years of preceding C (Group A). We elected to also study the protective effect of C against CC by extending the post-C observation period to 5 years and defined another set of CCdespiteC cases that were diagnosed 3 to 5 years of preceding C (Group B). **Results**: A total of 10,136 patients with either primary or metastatic colon cancer were identified between 1992 and 2004 at MCR. Of these, 2692 patients had undergone a total of 4743 colonoscopies at MCR. From this cohort, we identified 187 Cs in 145 patients as Group A and 124 Cs in 104 patients as Group B who developed CCdespiteC. There were subsets in which the CC was truly or possibly missed: no lesion was seen or treated in the colonic segment during the preceding C: 120 Cs in 100 patients for Group A (truly missed) and 60 Cs in 55 patients for Group B (possibly missed). Among the 44 endoscopists who performed at least 10 Cs in CC patients and for whom we were able to compute an average withdrawal time, the truly missed CC rate (truly missed CC per total CC cases) per endoscopist varied from 0% to 7.9% for Group A and from 0% to 7.7% for Group B. Among the endoscopists who missed at least one CC, 8-fold variation was observed for the truly missed lesion cohort. Moreover, a Pearson linear correlation for average withdrawal time versus truly missed cancer rate revealed R = -0.03 (with -0.32 and 0.27 as lower and upper bounds at a 95% confidence interval). **Conclusion**: The endoscopist, not the withdrawal time, is of critical importance given the 8-fold variation of truly missed CC rate for the interval of 90 days to 3 years. The absence of correlation between truly missed CC rate and average withdrawal time of each endoscopist suggests that some endoscopists can better detect lesions than others irrespective of the withdrawal time.

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Highly Sensitive and Specific Detection of Colorectal Cancer and Adenoma in Peripheral Blood By mRNA Expression Array Technology- Relation to Local Expression Patterns and Identification of Migrating Cell Population
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Background and aims: Screening and early diagnosis of colorecal cancer (CRC) is still challenging. Gene expression analysis of peripheral blood and colon migrating cell populations using high-density oligonucleotide microarray can contribute to the determination of distant blood markers of local pathophysiological alterations in colorectal diseases. Our aim was to identify peripheral blood (PBL) expression markers on migrating cells for objective classification of local colorectal diseases. Determination of correlation between disease specific PBL and local expression patterns and identification of cell compartments. Methods: Whole genomic gene expression profile (WGGEP) was evaluated from PBL samples of 11 patients with CRC, 11 with adenoma (>1 cm, AD), 11 with active inflammatory bowel disease (IBD) and 11 healthy (HE) controls. WGGEP analysis of biopsies (11 HE, 22 CRC, 20 AD and 21 IBD), then of the laser microdissected (LMD) epithelial, stromal and follicular tissue compartment was performed. For classification of samples Prediction Analysis of Microarrays were used. Chip results were confirmed by array real-time PCR on an independent sample set (45 patients) in the whole blood and in selected cases in mononuclear (MNC) and polymorphonuclear (PMNC) cell compartment, separately. Rectal biopsy microscopic analysis of male bone marrow (BM) transplanted females with colitis and normal histology was evaluated using immunofluorescent labeling (CD45) for the infiltration rate of PBL MNC cells. Results: CRC could be classified from all of the other observed groups by 86 % sensitivity and 86% specificity depending on the expression of 34 genes including septin 5, CD36. ADs were detected by 95% sensitivity and 91% specificity in relation to the HE using 21 classifiers including epidermal growth factor receptor, matrix metalloprotease 8, while IBD and HE could be discriminated using 13 genes (toll-like receptor 5, interleukin receptor 10B) by 94% sensitivity and 93% specificity. Array real-time PCR confirmation yielded a highly reproducible gene set that worked on an independent set of patients (sensitivity 87%, specificity 88%) and was present in MNC cells. Correlation to local expression pattern could be verified in the stroma of AD, CRC and IBD, but the highest recovery was in the follicles. The infiltration of male MNC CD45+ PBL cells was found in correlation with the degree of local inflammation in female BM transplants. Conclusions: Multivariate PBL expression markers were identified that reflect local colonic diseases. These markers could be confirmed in independent samples and in local LMD MNC cell compartments.

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A Simple Blood Test, Evaluating the Level of CD24 Protein, Can Detect Subjects with Adenomas
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Background: CD24 is a cell surface protein and P-selectin ligand, involved in cell adhesion and metastasis. Using gene expression array we have shown that CD24 expression is associated with colorectal cancer (CRC) (Gastro, 2006). The data was confirmed by IHC staining showing expression of CD24 in ~90% of adenomas and adenocarcinomas. Aim: To evaluate CD24 expression in peripheral blood lymphocytes (PBLs) from normal, adenoma and CRC subjects. Methods: Two independent sample populations were tested. The first pilot study included 203 consecutive subjects. Out of these, 143 samples were also evaluated by an external third party4. A second validation study included 167 subjects. Each consented person filled a detailed questionnaire, gave a blood sample, and underwent colonoscopy. PBLs were isolated and protein extracts were analyzed by Western blot using anti-CD24. Band intensities were scanned and tested for statistical significance using the MedCalc software. Sensitivity and specificity for CD24 was calculated using receiver operating characteristic (ROC) curves. The study was approved by the Israel Ministry of Health. Results: The sensitivity and specificity for distinguishing CRC from normal subjects in the pilot study was 70.5 and 83.3, and for the detection of adenomas was 84.2 and 73.5, respectively (95% CI). The results obtained in the external evaluation slightly varied, with a lower specificity (normal vs. CRC, 65; normal vs. adenoma, 76.7). Improved values for the detection of CRC were achieved in the validation study (Sen. 92.3; Spec. 83.8). The values for the detection of normal vs. CRC and adenomas were 77.1 and 86.8 (Fig.1). Conclusions: This blood test is the first of its kind to be able to detect adenomas. It can also successfully distinguish CRC from healthy subjects. CD24 may serve as a new potential and promising blood biomarker for the early detection and CRC surveillance.