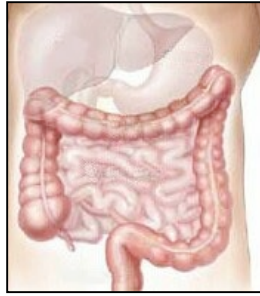


COLORECTAL CANCER RESEARCH UPDATES Month Ending July 10th, 2015



The following colorectal cancer research update extends from May 25th, 2015 – July 10th, 2015 inclusive and is intended for informational purposes only.

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1. New Drug Combination Extends Survival of Patients with Metastatic Colorectal Cancer (May 20/15)

An international clinical trial led by scientists at the Dana-Farber Cancer Institute has showed that TAS-102 lengthened the lives of metastatic colorectal cancer (mCRC) patients who had exhausted available standard treatments. The phase III study enrolled 800 patients with mCRC that was progressing despite previous treatment. Participants were randomly assigned to receive TAS-102 or a placebo pill. The drug combination not only extended patients' overall survival, but also delayed the advance of disease with very few side effects. The median survival period for patients receiving TAS-102 was 7.1 months, compared to 5.3 months for patients taking a placebo. The median time before the disease worsened was 5.7 months for the TAS-102 group and 4.0 months for the placebo group. According to the study authors, these results are especially impressive because half of these patients had just finished treatment with the standard class of chemotherapy agents - fluoropyrimidines (e.g. 5-fluorouracil [5-FU] or capecitabine [Xeloda]) but had failed to benefit from them. The fact that TAS-102 temporarily halted the disease in many of these patients suggests that it operates through a different biochemical pathway than 5-FU, and therefore may serve as an alternative to standard therapy. 5-FU works by blocking an enzyme (thymidylate synthase) that cancer cells need for survival. The cancer cell-killing component of TAS-102, a drug known as trifluridine, by contrast, integrates into cancer cell DNA and prevents the cells from metabolizing nutrients. The next step will be to test TAS-102 in combination with other drugs that are customarily used in conjunction with 5-FU, and compare results.

Mayer, Robert J. et al. "Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer." *N Engl J Med* 2015; 372:1909-1919. May 14, 2015. DOI: 10.1056/NEJMoa1414325.

<http://www.endonurse.com/news/2015/05/new-drug-combination-extends-survival-of-patients.aspx>

2. Genomic Marker Predicted Anti-PD-1 Response in Colorectal Cancer (May 29/15)

According to data from a phase II study, mismatch repair-deficient tumors which lack the ability to repair DNA were found to be highly responsive to checkpoint blockade with the anti-programmed death 1 (PD-1) drug pembrolizumab. The study included 3 cohorts of patients assigned to pembrolizumab 10 mg/kg every 2 weeks. Cohort A included 25 patients with mismatch repair-deficient colorectal tumors, cohort B included 25 patients with mismatch repair-proficient colorectal tumors, and cohort C included 21 patients with non-colorectal mismatch repair-deficient tumors. Patients with mismatch repair-proficient colorectal tumors (cohort B) had poor responses to checkpoint blockade, including a 0% response rate and 16% disease control rate. In comparison, patients with mismatch repair-deficient colorectal tumors (cohort A) had excellent responses, including a 62% objective response rate and 92% disease control rate. According to the investigators, the responses seen among patients with mismatch repair-deficient tumors were durable and ongoing. Mismatch repair deficiency is represented in approximately 4% to 5% of many tumor types and is easily determined using a commercially available test.

Le, Dung T. et al. "PD-1 blockade in tumors with mismatch repair deficiency". 2015. Presented during Clinical Science Symposium, Immunotherapy for Every Patient: Check Your Enthusiasm, at 2015 ASCO Annual Meeting.

<http://www.cancernetwork.com/asco-2015-colorectal-cancer/genomic-marker-predicted-anti-pd-1-response-colorectal-cancer>
<https://clinicaltrials.gov/show/NCT01876511>

3. Aspirin Exposure after Colorectal Cancer Diagnosis Associated with Improved Survival (June 1/15)

Aspirin exposure after the diagnosis of colorectal cancer (CRC) increased cancer-specific survival and overall survival in a cohort of 25,644 Norwegian patients. Of this study sample, 6,109 patients were defined as exposed to aspirin after cancer diagnosis. Results showed that during a median follow-up of 2.2 years, there was a total of 2,088 deaths among aspirin users, of which 1,172 were CRC-specific. Among non-aspirin users, there was a total of 7,595 deaths, of which 6,356 were CRC-related. In multivariate analysis, aspirin exposure after the diagnosis of CRC was independently associated with improved CRC-specific survival and overall survival. The findings of this study suggest that aspirin should be further evaluated as secondary prevention in patients with CRC.

Bains S, Mahic M, Cvancarova M, et al. "Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study". *J Clin Oncol*. 2015;33:(suppl; abstr 3504).

<http://www.oncologynurseadvisor.com/asco-2015-annual-meeting/aspirin-exposure-after-colorectal-cancer-diagnosis-associated-with-improved-survival/article/417665/>

4. Immunomedics Reports Labetuzumab Govitecan is Active in Relapsed Metastatic Colorectal Cancer (June 2/15)

An interim analysis of a mid-stage clinical study showed that labetuzumab govitecan, a novel antibody-drug conjugate (ADC) being developed by the biopharmaceutical company Immunomedics, produced encouraging survival results in mCRC patients previously treated with at least one prior irinotecan-containing regimen. For the 33 patients who received labetuzumab govitecan, the interim median progression-free survival (PFS), a measure of the length of time a patient is living without the disease getting worse from the beginning of treatment, was 4.4 months, with 22% of patients still benefiting from their cancer not progressing. In terms of treatment response, in 32 patients with at least one evaluation following treatments, 1 patient had a partial response and 24 patients reported stable disease as their best response, to give a combined disease control rate of 78%.

Labetuzumab govitecan was created by conjugating the moderately-toxic drug, SN-38, to labetuzumab, a humanized antibody that recognizes the carcinoembryonic antigen (CEA; CEACAM5 or CD66e) expressed in many solid cancers, including >90% of CRCs. SN-38 is the active metabolite of irinotecan (Camptosar), which is used to treat certain solid cancers, particularly mCRC, as part of combination therapies. In clinical trials, labetuzumab govitecan has been well tolerated by a majority of patients. At the optimal once-a-week doses of 8 and 10 mg/kg, grades 3 and 4 adverse events with occurrence of 5% or more included neutropenia (5% for both dose levels) and mild diarrhea (5% in the 8 mg/kg group only). Despite repeated dosing, no antibody against labetuzumab or its SN-38 conjugate was detected in blood samples from 74 patients over a 16-month period.

Dotan E, Starodub A, Berlin J, Lieu CH, Guarino MJ, Marshall J, Hecht JR, et al. "A new anti-CEA-SN-38 antibody-drug conjugate (ADC), IMMU-130, is active in controlling metastatic colorectal cancer (mCRC) in patients (pts) refractory or relapsing after irinotecan-containing chemotherapies: Initial results of a phase I/II study". J Clin Oncol 33, 2015 (suppl; abstr 2505)

<http://www.virtual-strategy.com/2015/06/02/immunomedics-reports-labetuzumab-govitecan-active-relapsed-metastatic-colorectal-cancer#axzz3fE3L4wi3>

5. Liver-Directed Therapies Increase Survival in mCRC (June 12/15)

The following is a summary of two studies presented at the annual American Society of Clinical Oncology meeting. These studies both address the value and timing of liver-directed therapies in the management of unresectable hepatic metastases in CRC patients. They support the incorporation of liver-directed therapy in the management of hepatic mCRCs and broaden the range of therapies available to patients with these incurable cancers.

- 1) To better define the role of liver-directed therapy, Dr. Theo Ruers conducted a study in which patients with hepatic metastatic disease from CRC were randomly assigned to receive treatment with either chemotherapy alone or chemotherapy augmented by radiofrequency ablation (RFA) to the liver lesions. A statistically significant improvement in overall survival (OS) resulted, with average OS of 45.6 months when the RFA was incorporated into treatment vs. 40.5 months when chemotherapy was used alone. The progression-free survival (PFS) was also significantly improved in the RFA group.
- 2) Dr. Peter Gibbs conducted a study in which CRC patients with liver metastasis were randomly assigned to receive first-line treatment of chemotherapy alone or chemotherapy along with selective internal radiation therapy (SIRT) to the liver lesions. SIRT consisted of yttrium-90 (Y-90) resin microspheres. Overall PFS was not statistically improved with the addition of SIRT. However, median PFS in the liver was significantly extended with the addition of SIRT. The FS was 20.5 months in the SIRT group vs. 12.6 months in the control group.

Ruers T, Punt CJA, van Coevorden F, et al. "Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC)." Program and abstracts of the American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2015; Chicago, Illinois. Abstract 3501.

Gibbs P, Heinemann V, Sharma NK, et al. "SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC)." Program and abstracts of the American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2015; Chicago, Illinois. Abstract 3502.

<http://www.medscape.com/viewarticle/846248>

6. Improved OS, PFS Demonstrated by TAS-102, Regardless of KRAS Status (Jul. 3/15)

Findings from a subgroup analysis of the phase III RECURSE trial have shown that TAS-102 is associated with significantly improved OS and PFS compared with placebo in patients with KRAS wild-type (WT) and mutant mCRC, along with a favorable safety profile. The overall survival benefit in patients with KRAS mutant tumors did not reach statistical significance.

The RECURSE trial evaluated the efficacy and safety of TAS-102 in 800 mCRC patients who were refractory to, or intolerant of, standard therapies. Patients were required to have undergone ≥2 prior lines

of standard chemotherapy. Patients with KRAS wild-type tumors must have had prior anti-EGFR treatment. The trial showed a significant improvement in OS with a median of 7.1 months in TAS-102 patients compared with 5.3 months with placebo. The PFS was a median of 2.0 versus in the treatment group vs. 1.7 months in the placebo group. KRAS wild-type tumors were identified in 394 (49.3%) patients. KRAS mutated tumors were seen in 406 (50.8%) patients. Of the 534 patients treated with TAS-102, KRAS wild-type was seen in 260 patients (48.7%) and mutated in 274 patients (51.3%). In all, 266 patients were given placebo of which 273 (51.3%) and 132 (49.6%) patients had tumors that were KRAS wild-type and mutated, respectively. Researchers reported that patients with KRAS wild-type tumors demonstrated a median OS of 8.0 months when treated with TAS-102 compared with 5.7 months in when receiving placebo. PFS was a median 2.1 months for patients treated with TAS-102 versus 1.7 months in the placebo group. Researchers reported no overall differences in incidence of adverse events across patient subgroups based on KRAS status. No significant differences were seen according to mutational status regarding the safety profile that accompanied treatment with TAS-102. Patients receiving TAS-102 with KRAS mutant tumors had a higher incidence ($\geq 5\%$) compared to patients with KRAS wild type, respectively, of diarrhea (35.2% vs 28.5%), asthenia (21.6% vs 14.6%), and decreased appetite (43.2% vs 34.6%). Patients with KRAS wild-type tumors had a higher incidence of decreased neutrophil (30.4% versus 25.3%) and white blood cell count (31.5% versus 23.4%).

Hochster H, Hager S, Pipas JM, et al. "KRAS and BRAF gene subgroup analysis in the Phase 3 RECURSE trial of TAS-102 versus placebo in patients with metastatic colorectal cancer." *Ann Oncol.* 2015;26 (suppl 4; O-010).

Mayer RJ, Van Cutsem E, Falcone A, et al. "Randomized trial of TAS-102 for refractory metastatic colorectal cancer." *N Engl J Med.* 2015;372(20):1909-1919.

<http://www.onclive.com/conference-coverage/2015-world-GI/improved-os-pfs-demonstrated-by-tas-102-regardless-of-kras-status>

7. Second-line cetuximab active beyond progression in quadruple wild-type patients with mCRC (Jul. 4/15)

The CAPRI-GOIM study investigated the efficacy of cetuximab plus FOLFOX chemotherapy as second-line treatment for patients with mCRC that had progressed following FOLFIRI chemotherapy plus cetuximab. CAPRI-GOIM is a phase II trial enrolling 340 patients with mCRC and KRAS exon 2 WT tumours. All patients received standard first-line treatment of FOLFIRI plus cetuximab until disease progression or unacceptable toxicity. Following first-line treatment, patients experiencing disease progression were randomised to receive second-line treatment of FOLFOX plus cetuximab (Arm A) or solely FOLFOX (Arm B). The primary endpoint of the study was progression-free survival (PFS) and secondary endpoints were overall survival (OS), response rate and safety. The data showed an advantage in PFS favouring arm A, but did not reach statistical significance. Patient characteristics were described to account for this result. Next generation sequencing (NGS) was used to identify genes of interest in patients' primary tumours, including the KRAS, NRAS, BRAF and PIK3CA genes. Two distinct patient populations were detected: one that was multiple WT and normal for all 4 genes and another that were mutated in at least 1 of these genes. In patients with at least 1 mutation, a detrimental effect from FOLFOX plus cetuximab in progression-free survival, response rate and overall survival was observed. Conversely, the quadruple WT population showed significantly prolonged PFS, and improved OS and response rates with second-line cetuximab plus FOLFOX. This suggests that patients with tumours that are multiple WT are most likely to be EGFR-dependent. CAPRI is the first randomised phase II study to evaluate cetuximab as a second line treatment beyond progression in mCRC patients. Results suggest that tumours with multiple wild-type KRAS, NRAS, BRAF and PIK3CA genes are likely to benefit from chemotherapy plus cetuximab.

Ciardello, F. et al. "Clinical activity of FOLFIRI plus cetuximab according to extended gene mutation status by next-generation sequencing: findings from the CAPRI-GOIM trial." *Ann Oncol.* 2014 Sep;25(9):1756-61. doi: 10.1093/annonc/mdu230. Epub 2014 Jun 18.

<http://medicalxpress.com/news/2015-07-second-line-cetuximab-quadruple-wild-type-patients.html>

8. Encorafenib-Based Regimens Show Promising Clinical Activity In BRAF-Mutant Colorectal Cancer Patients (Jul. 6/15)

A phase 1b trial, as well as its preliminary 100-patient randomized phase II expansion, have tested the combination of encorafenib (RAF inhibitor) and cetuximab (EGFR inhibitor) with or without the addition of alpelisib (BYL719) 1 (investigational PI3K inhibitor) in patients with BRAF-mutant colorectal cancer (BRAFmut CRC). Findings indicate that these combinations can be administered with good tolerability and show promising clinical activity in this patient population with high unmet medical needs. Preliminary phase II results show an objective response rate (complete or partial response) and disease control rate (complete or partial response or stable disease) of 29% and 81%, respectively, for patients receiving the combination of encorafenib and cetuximab. Rates were 35% and 79%, respectively, for patients receiving the combination of encorafenib, cetuximab and alpelisib. Across both treatment groups, most adverse events were grade 1 or 2 with few grade 3 or 4 adverse events. The most frequent treatment related adverse events across all grades for the encorafenib + cetuximab group were fatigue (36%), nausea (31%), lipase increased (24%), diarrhea (21%) and decreased appetite (21%). Adverse events consisted of diarrhea (39%), nausea (37%), fatigue (33%) and hyperglycemia (31%) for the encorafenib +

cetuximab + alpelisib group. These results are consistent with the Phase 1b portion of the trial and are encouraging when compared to currently available therapies for BRAFmut CRC patients.

RAF is a key protein kinase in the MAPK signaling pathway that regulates several essential cellular activities including proliferation, migration, survival and angiogenesis. Inappropriate activation of this pathway has been shown to occur in many cancers, including CRC. Encorafenib is a selective, small molecule, oral inhibitor which targets the RAF enzyme in this pathway.

<http://news.sys-con.com/node/3356137>

SURGICAL THERAPIES

9. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study (Jul. 5/15)

Abdominoperineal resection is the standard treatment for patients with distal T2 or T3 rectal cancers. However, this procedure can be extensive and mutilating. This prospective observational trial assessed whether high-dose radiotherapy and chemotherapy, followed by observation (watchful waiting) was successful for non-surgical management of low rectal cancer. Patients with primary, resectable, T2 or T3, N0–N1 adenocarcinoma in the lower 6 cm of the rectum were given chemoradiotherapy (60 Gy in 30 fractions to tumour, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil 300 mg/m²) every weekday for 6 weeks. After treatment, patients were referred to the observation group (watchful waiting) or standard surgery. Patients under observation were followed up with endoscopies and selected-site biopsies, with surgical resection given for local recurrence. The primary endpoint was local tumour recurrence 1 year after referral to the observation group. 55 patients were enrolled in this Danish study. Of 51 patients who were eligible, 40 had clinical complete response and were allocated to the observation group. Median follow-up for local recurrence in the observation group was 23.9 months. Local recurrence in the observation group at 1 year was 15.5%. The most common acute grade 3 adverse event during treatment was diarrhoea, which affected four (8%) of 51 patients. Sphincter function in the observation group was excellent, with 18 (72%) of 25 patients at 1 year and 11 (69%) of 16 patients at 2 years reporting no faecal incontinence at all. The most common late toxicity was bleeding from the rectal mucosa. Grade 3 bleeding was reported in two (7%) in 30 patients at 1 year and one (6%) of 17 patients at 2 years. There were no unexpected serious adverse reactions or treatment-related deaths. This study shows that high-dose chemoradiotherapy and observation may be a safe alternative to abdominoperineal resection for patients with distal rectal cancer.

Appelt, Ane L. et al. "High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study." *The Lancet Oncology*. DOI: [http://dx.doi.org/10.1016/S1470-2045\(15\)00120-5](http://dx.doi.org/10.1016/S1470-2045(15)00120-5). Epub 2015 July 5.

[http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(15\)00120-5/fulltext?rss=yes](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00120-5/fulltext?rss=yes)

10. Managing synchronous liver metastases from colorectal cancer: A multidisciplinary international consensus (June 30/15)

An international panel of multidisciplinary experts convened to develop recommendations for managing patients with CRC and synchronous liver metastases (CRCLM). CRCLM is defined as liver metastases detected at or before diagnosis of the primary CRC. Early and late metachronous metastases are defined as those detected ≤ 12 months and > 12 months after surgery, respectively. The prognosis is poorer for synchronously detected metastases than for metachronous ones. However, advances in diagnosis, systemic treatment and surgery have improved outcomes. To provide information on potential curability, use of high-quality contrast-enhanced computed tomography (CT) before chemotherapy is recommended. Magnetic resonance imaging (MRI) is increasingly being used alongside CT in difficult situations. To evaluate operability, radiology should provide information on: nodule size and number, segmental localization and relationship with major vessels, response after neoadjuvant chemotherapy, non-tumoral liver condition and anticipated remnant liver volume. Pathological evaluation should assess response to preoperative chemotherapy for both the primary tumour and metastases, and provide information on the tumour, margin size and micrometastases. The treatment strategy depends on resectability and symptoms of liver metastases and the primary tumour. The consensus is for chemotherapy before surgery in most cases. When the primary CRC is asymptomatic, liver surgery may be performed first. When CRCLM are unresectable, the goal of preoperative chemotherapy is to downsize tumours to allow resection. Hepatic resection should not be denied to patients with stable disease after optimal chemotherapy, provided an adequate liver remnant with inflow and outflow preservation remains. Evaluation by a hepatobiliary multidisciplinary team is key to optimizing outcomes.

RADIATION/INTERVENTIONAL RADIOLOGY

11. Addition of Selective Radiation Improves Liver Survival in Colorectal Cancer Metastases (May 30/15)

The SIRFLOX study is an international, multicenter, open-label, controlled trial with an enrolment of 530 chemotherapy-naïve patients with non-resectable, liver-only or liver-dominant mCRC. These patients were randomly assigned to receive mFOLFOX6 with or without bevacizumab (group A) or mFOLFOX6 plus selective internal radiation therapy (SIRT) administered once with cycle 1 with or without bevacizumab in cycle 4 (group B) until disease progression. The addition of SIRT, using Y-90 resin microspheres, to FOLFOX-based first-line chemotherapy did not improve overall PFS. However, median liver PFS was significantly prolonged. Results showed that at a median follow-up of 36.1 months, median overall PFS was 10.2 months in group A vs. 10.7 months in group B. However, median liver PFS was 12.6 months in group A vs. 20.5 months in group B. As such, addition of selective radiation achieved a 7.9 month improvement in median PFS in the liver, representing a 31% reduction in risk of disease progression in the liver with no negative impact on duration of systemic therapy, and had toxicities that were acceptable and as predicted. Grade 3 or higher adverse events occurred in 73.4% of patients in group A vs. 85.4% of those in group B. The most common toxicities were hematologic and gastrointestinal. Analyses on overall survival using data from SIRFLOX and two other ongoing trials in this disease setting are being conducted.

Gibbs P, Heinemann V, Sharma NK, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC). *J Clin Oncol*. 2015;33:(suppl; abstr 3502).

<http://www.cancertherapyadvisor.com/asco-2015/asco-selective-radiation-chemotherapy-sirt-colorectal-cancer-liver-metastases/article/417593/>

12. Radiofrequency Ablation for Liver Mets Improved Survival in CRC (June 5/15)

Treating patients with unresectable CRC liver metastases using radiofrequency ablation and systemic chemotherapy resulted in an improved long-term OS compared with the use of chemotherapy alone, according to the 10-year OS results of the phase II EORTC-NCRI-CCSG-ALM Intergroup 40004 (CLOCC) study. Although radiofrequency ablation is increasingly used in patients with unresectable CRC liver metastases, prospective data backing this method in a defined therapeutic setting has been scarce. This trial included 119 patients randomly assigned to chemotherapy alone or radiofrequency ablation plus chemotherapy. The chemotherapy regimen used in the study was 6 months of FOLFOX, with bevacizumab added later. Patients could undergo resection when chemotherapy converted unresectable disease to resectable disease. The primary endpoint of the study was 30-month OS of greater than 38% for the combined treatment group. At a median follow-up of 4.4 months, the 30-month OS rate for combined treatment was 61.7% vs. 57.6% for chemotherapy alone. There was also a significant improvement in PFS, with a median survival of 16.8 months for combined treatment vs. 9.9 months for chemotherapy alone. The updated results were presented after a median follow-up of 9.7 years. At this time, the median PFS was 16.82 months for combined treatment vs. 9.92 months for chemotherapy alone. The median OS was 45.6 months for combined treatment vs. 40.54 months for chemotherapy alone. The current OS status shows that 35% of patients were still alive at last contact in the combined treatment group vs. 10% in the chemotherapy group. Almost all patients, when they died, died of progressive disease. These findings encourage the use of ablative techniques as a treatment modality in patients with unresectable CRC liver metastases.

<http://www.cancernetwork.com/asco-2015-colorectal-cancer/radiofrequency-ablation-liver-mets-improved-survival-crc>

SCREENING

13. Fecal immunochemical testing may reduce colorectal cancer mortality (May 27/15)

A prospective cohort study followed over 1.1 million Taiwanese people between the ages of 50 and 69 years as they underwent fecal immunochemical testing screening between 2004 and 2009. Researchers then compared CRC-specific mortality for a screened group with an unscreened group. Results showed

that fecal immunochemical testing screening reduced CRC-specific mortality by 62% with a maximum follow-up of 6 years. After adjustments for a self-selection bias, researchers found that screening reduced cancer-specific mortality by 10%. Population-based fecal immunochemical testing screening for CRC has indeed demonstrated a significant reduction in CRC mortality despite a short follow-up time. Researchers plan to continue following-up this large cohort to assess the long-term effect of fecal immunochemical testing screening.

Chiu, H.-M., Chen, S. L.-S., Yen, A. M.-F., Chiu, S. Y.-H., Fann, J. C.-Y., Lee, Y.-C., Pan, S.-L., Wu, M.-S., Liao, C.-S., Chen, H.-H., Koong, S.-L. and Chiou, S.-T. (2015), "Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program." *Cancer*. doi: 10.1002/cncr.29462

<http://www.oncologynurseadvisor.com/headlines/fecal-immuno-chemical-colorectal-cancer-testing-mortality/article/416849/>

14. Younger first-degree relatives of colorectal cancer patients less likely to have colonoscopy (June 9/15)

First-degree relatives younger than the conventional screening age of 50 are less likely than adults aged >50 to have had a colonoscopy, according to recent study data. Aiming to learn whether younger first-degree relatives of CRC patients are undergoing screening colonoscopy according to the current guideline from the American College of Gastroenterology, which recommends screening begin at age 40 if the relative is diagnosed before age 60, investigators performed a U.S. population-based study. 26,064 eligible respondents were identified for whom the colonoscopy rate was 16.5% in 2005 vs. 49.1% in 2010. Among the 2,470 respondents who reported a family history of CRC, 45.6% underwent colonoscopy (25.2% in 2005 and 65.8% in 2010 vs. 19% and 57%, respectively, for non-first-degree relatives). First-degree relatives were 70% more likely to have a colonoscopy compared with non-first-degree relative. However, those aged 40-49 years were less likely to have a colonoscopy compared with those aged >50. Among first-degree relatives aged 40-49 years, the colonoscopy rate was 38.3% vs. 69.7% for those aged >50 years. This study shows the need for increasing screening rates in this younger subgroup, particularly first-degree relatives <50 years because of the recent increase in CRC in this age group.

Tsai M, et al. "Younger first-degree relatives of colorectal cancer patients less likely to have colonoscopy." *Prev Chronic Dis*. 2015;doi:10.5888/pcd12.140533.

<http://www.healio.com/gastroenterology/oncology/news/online/%7B938fc4af-5a67-43c5-af2c-bc92565a7a5b%7D/younger-first-degree-relatives-of-colorectal-cancer-patients-less-likely-to-have-colonoscopy>

OTHER

15. Study shows colorectal cancer genetically different in older and younger patients (May 29/15)

While the overall rate of CRC is declining, CRC among younger patients is increasing. Previous studies have shown that CRC in patients <50 years old tends to be more aggressive than in older patients. A University of Colorado Cancer Center study offers early evidence of genetic differences between CRC in young and old patients, possibly pointing toward different treatments and strategies in combating the young form of the disease. The study compared the genetics of 5 CRC tumors from younger patients (median age 31) to 6 tumors from older patients (median age 73), sequencing 45 million "reads" from each tumor. Researchers then explored the data for significant differences between groups. They observed differences in two important gene signaling pathways, PPAR and IGF1R, which are involved in regulating cell development, metabolism, and growth. Alterations in these signaling pathways have been implicated in the development of several types of cancer. In addition, the study showed that younger CRC tumor samples were enriched for pathways responsible for metabolizing drugs. This suggests that younger people may metabolize chemotherapies differently than older patients. It may also explain why traditional chemotherapy treatments tend to be less effective in younger mCRC patients. These findings will need to be validated in a larger patient population.

Pitts, Todd M. et al. "Emerging transcriptional landscape and putative therapeutic strategies in young patients with metastatic colorectal cancer (CRC)." *J Clin Oncol* 33, 2015 (suppl; abstr e14627)

<http://medicalxpress.com/news/2015-05-colorectal-cancer-genetically-older-younger.html>

16. Targeting dormant cells may halt colorectal cancer spread (June 30/15)

Conventional treatments for CRC sometimes have poor outcomes because by the time the disease is detected, cancerous cells have spread to nearby organs. Tumour cells can lie dormant and undetected for years, until triggered to grow into secondary tumors that then become the cause of death. An Australian study has targeted dormant CRC cells rather than active tumor cells as a treatment option for CRC. Previous research has already established that crypt base stem cells (CRCs) help to regenerate the epithelium or lining of the gut when it becomes damaged. To do this, these cells allow "Wnt" signals through their surface receptors into their cell interior. The receptors that allow passage to Wnt signals are called "Frizzled," and there are 10 different types. This study has characterized the particular Frizzled receptor, Frizzled7, which allows passage to Wnt signals in the CRCs to trigger cancer. Researchers have found that if Frizzled7 is knocked out while cells are in a dormant state, they are not able to make the tumor grow. The consequences of these findings represent a shift in the targeted management of cancers. Subsequent steps will involve finding a way to target Frizzled7 and develop antibody treatments that work with current therapies.



Researchers have found a way to control the stem cell behaviour that causes the spread of CRC

Flanagan, Dustin J. et al., "Frizzled7 functions as a Wnt receptor in intestinal epithelial Lgr5+ stem cells." Stem Cell Reports, doi:10.1016/j.stemcr.2015.03.003, published online 12 May 2015.

<http://www.medicalnewstoday.com/articles/296051.php>

NUTRITION & HEALTHY LIFESTYLE

17. Milk Thistle Extract Stops Colorectal Cancer Stem Cells From Growing Tumors (May 29/15)

A University of Colorado Cancer Center study has shown that orally administering the chemical silibinin, purified from milk thistle, slows the ability of CRC stem cells to grow the disease in mouse models. Tumours in silibinin fed mice had fewer cancer stem cells, were smaller in size, had lower metabolisms, and showed decreased growth of new blood vessels. When stem cells from these tumours were re-injected into new mice, cells failed to develop equally aggressive tumours even in the absence of silibinin exposure. Silibinin is a nontoxic, potentially chemopreventive agent derived from milk thistle seeds. Previous data has shown that, in cell cultures, silibinin affects cell signalling associated with the formation and survival of CRC stem cells. The current study extends this promising line of research into mouse models. Researchers will continue to investigate the molecular mechanisms, cell culture, and animal model effects of silibinin toward a likely human clinical trial of silibinin in cancer preventative and/or treatment settings.

University of Colorado Denver. "Oral milk thistle extract stops colorectal cancer stem cells from growing tumors." ScienceDaily. ScienceDaily, 20 April 2015. <www.sciencedaily.com/releases/2015/04/150420144350.htm>.

<http://www.theepochtimes.com/n3/1372576-oral-milk-thistle-extract-stops-colorectal-cancer-stem-cells-from-growing-tumors/>

18. Higher Vitamin D Levels Linked to Improved Colorectal Cancer Survival (May 31/15)

Increased concentrations of 25-hydroxyvitamin D were associated with significantly improved overall survival rates in a group of mCRC patients treated as part of the phase III Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) 80405 trial. Previous research has shown that vitamin D inhibits cell proliferation and angiogenesis and induces cell differentiation and apoptosis, as well as having anti-inflammatory effects. It has also been shown that higher pre-diagnosis levels of plasma 25-hydroxyvitamin D are associated with significant improvements in OS. In the current analysis, researchers evaluated 1,043 patients from the CALGB/SWOG 80405 trial, which randomly assigned patients to chemotherapy plus bevacizumab, cetuximab, or both. Plasma vitamin D levels were measured at baseline, and information on dietary and lifestyle behaviors were collected from patient questionnaires. Patients were divided into quintiles based on vitamin D levels, with the median vitamin D value in the highest quintile being 27.5 ng/mL and 8.0 ng/mL in the lowest quintile. Patients with vitamin D levels in the highest quintile had a significantly improved OS compared with patients in the lowest quintile, with a median OS of 32.6 months vs. 24.5 months. A similar trend was observed for PFS, with a median survival of 12.2 months for patients with the highest vitamin D levels vs. 10.1 months for those with the lowest levels. A concern often raised is that higher vitamin D levels may be acting as a surrogate for other healthy behaviors or more favorable disease. However, study leads had access to detailed patient and tumor information, as well as data on diet and lifestyle factors, which allowed for a multivariable analysis that adjusted for potential confounding factors. In the multivariable analysis, patients with the highest levels of vitamin D had a 35% improvement in OS and a 21% improvement in PFS compared to patients with the lowest levels. A phase II randomized trial to evaluate the impact of vitamin D in conjunction with chemotherapy is currently ongoing.

Ng K, Meyerhardt JA, Wu K, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J Clin Oncol*. 2008;26:2984-2991.

<http://www.cancernetwork.com/asco-2015-colorectal-cancer/higher-vitamin-d-levels-linked-improved-colorectal-cancer-survival>

19. Lifestyle recommendations: can they prevent colorectal cancer risk? (June 11/15)

Large variations in survival exist among CRC patients that might be related to differences in lifestyle. Abundant research has shown that CRC risk is influenced by lifestyle characteristics such as smoking, high alcohol consumption, diets low in fibre and rich in processed meats, low physical activity and high body fatness. In 2007, the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) formulated lifestyle recommendations for cancer prevention. These recommendations include the maintenance of a healthy body weight throughout one's lifetime, being physically active, eating a mostly plant-based diet, avoiding the consumption of highly preserved foods, preserved meats, sugary drinks and other foods that promote weight gain, and drinking alcohol in moderation, if any. A special recommendation for mothers to aim to exclusively breastfeed their children up to six months was included, and for cancer survivors to follow the recommendations for cancer prevention. The latter was based in the data on cancer prevention, because studies on the link of dietary and lifestyle factors on cancer survival were still scarce.

A few years ago, an index score was developed to reflect adherence to the WCRF/AICR recommendation. The first studies using this score were conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC). This is a prospective study of over half a million participants across ten European countries with the aim of ascertaining how lifestyle, metabolic and genetic factors may influence the risk of developing cancer and other chronic diseases. It showed that participants with higher WCRF/AICR index scores, reflecting a lifestyle in concordance with the WCRF/AICR recommendations, had 18% lower risk of having any type of cancer, 27% lower risk of CRC, and lived longer than participants with the lowest scores. Subsequent research has confirmed these findings: despite differences in study populations, overall greater adherence with the WCRF/AICR recommendations predicts a lower cancer risk.

One of the research questions recently explored in EPIC is whether people with lifestyle in concordance with the WCRF/AICR recommendations live longer after cancer diagnosis than people whose lifestyle is less concordant with the recommendations. WCRF/AICR scores were calculated in 3,292 EPIC participants who had been diagnosed with CRC 6.4 years later on average. The score was constructed using data on lifestyle and body weight assessed before cancer diagnosis. About 4 years after CRC diagnosis, 1,113 patients had died, from which 872 deaths were due to CRC. CRC patients with a higher WCRF/AICR score had 30% lower risk of dying from CRC compared to those with lower adherence. Having a healthy body weight (not being obese or overweight), and having a diet rich in plant foods were the factors that better predicted survival in these CRC patients.

This study has several limitations. First, lifestyle and body weight were assessed only at enrolment in EPIC, before cancer diagnosis, and may have changed during follow-up, especially after cancer diagnosis. Lifestyle in patients during cancer treatment was also not investigated. Nevertheless, these findings have shown that a healthy lifestyle during adulthood, in line with the WCRF/AICR recommendations may contribute to cancer prevention and increase survival after CRC diagnosis.

20. Don't Let Risk of Cancer Ruin Your Summer Grilling (June 26/15)

While the grill can provide an alternative to cooking on the stove, you must be careful to not overcook foods which may increase the risk of consuming too many carcinogens. Certain cancers of the colon are linked to these carcinogens. Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are chemicals that are created when cooking certain meats on the grill. Animal studies show that HCAs and PAHs are mutagenic and so cause changes in DNA and may increase the risk of cancer after they are metabolized in the body. HCAs are caused when the amino acids, sugars and creatine (a substance found in muscle meat) react to the types of high temperatures from an open flame or pan frying. These changes can be visually detected in the meat when the flesh browns and eventually blackens. A higher level of HCAs forms when the flesh chars. Meanwhile, PAHs begin to develop when the fat from the flesh drips onto the fire, coals or heating element. The flare caused by the drip creates smoke. That smoke contains PAHs that eventually stick to the meat. Foods that can develop carcinogens when cooked at high temperatures, anything higher than 300 degrees Fahrenheit, include: fish and shellfish, poultry (chicken, turkey, duck), beef, lamb, pork and veal. Smoking, curing and salting meats also raises cancer risk because of the damaging effects of these products in our cells.

In addition to the carcinogens created on the grill, processed meats and red meats are also strongly linked to an increased risk in developing certain cancers. The AICR recommends limiting red meat to no more than 18 ounces weekly. One of the reasons for limiting meat is the type of iron it contains. About 40% of the iron in meat is heme iron. Nonheme iron comprises the rest of the iron in meat. Heme iron is absorbed at much higher levels than nonheme iron, and is also linked to CRC. In addition, take caution consuming processed meats, such as hot dogs, salami, ham, bacon and sausages, because they contain higher levels of nitrates and other chemicals used to preserve them.

There are certain ways to reduce the risk of creating too many HCAs and PAHs in foods such as marinating, sealing food in aluminum foil and precooking. Here are some tips on cooking food safely to limit cancer risk:

- **Marinate:** Studies show marinating meats, poultry and fish will reduce the formation of HCAs significantly. Use a mixture of vinegar or lemon juice, various herbs and spices, and marinate for at least 30 minutes.
- **Precook your meat:** Precooking will lessen the time the meat is on the grill, reducing the amount of PAHs. Precook in the oven or stove and finish it on the grill for flavor.
- **Safer alternatives:** Limit consumption of beef burgers and hot dogs, and choose nonmeat options such as veggie burgers, veggie kebabs and grilled tofu. Also, fish does not require the degree of cooking that meats do.
- **Foil it:** Place a foil sheet on the grill first to protect foods from direct exposure to flames. This way, the smoking that occurs when the fat and other juices drip onto the flame is eliminated.
- **Cook over a low flame:** Cooking at lower temperatures avoids charring associated with the formation of HCAs and PAHs.

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<http://www.asbestos.com/blog/2015/06/26/reducing-cancer-causing-chemicals-grilling/>

21. Daily consumption of nuts found to decrease risk of developing cancer!

Research continues to grow to support the many health benefits that nuts provide our bodies. A recent study explores nuts' ability to prevent cancer. Researchers from the Mayo Clinic in Rochester, Minnesota conducted a review and meta-analysis of 36 observational studies that included 30,708 patients. The results of the study suggest that nut consumption may be associated with reduced risk of cancers, including colorectal, endometrial and pancreatic cancers. Aligning with the known beneficial effect of nuts

on heart diseases, this study may imply that individuals interested in making better food choices to reduce the risk of cancer and heart disease can consider consuming nuts, after considering the caloric and fat contents of different types of nuts. Another series of large studies followed 42,498 men and found that those who consumed more nuts were less likely to die at any given age of cancer or heart disease. Furthermore, a clinical trial conducted in Spain found that those who ate a Mediterranean diet and consumed extra nuts had lower death rates. According to another study completed by Harvard's Dana Farber Cancer Institute, those who ate a handful of nuts daily were 20% less likely to die from any cause over a 30 year time period. The reduction in mortality risk was similar when considering peanuts or tree nuts such as walnuts, hazelnuts, almonds, pecans, pistachios or pine nuts. Nuts have been shown to be connected with lower risk of heart disease, type 2 diabetes, colon cancer, gallstones and diverticulitis. Daily nut intake has also been shown to reduce cholesterol levels, oxidative stress, inflammation, adiposity, and insulin resistance.

Oxford University Press USA. "Nut consumption associated with reduced risk of some types of cancer." ScienceDaily. ScienceDaily, 16 June 2015. <www.sciencedaily.com/releases/2015/06/150616114247.htm>.

<http://news.therawfoodworld.com/nuts-for-cancer/>

22. Food Fighters: From apples to flaxseeds, certain foods work to fight cancer

Many foods already associated with a healthy diet could help prevent some types of cancer. Based on research from the AICR, this list includes high-fiber foods that fight colon and rectal cancers in addition to fruits and vegetables that prevent weight gain. Many of the foods on the list also contain antioxidants - molecules that fight free radicals, which are compounds that can damage cells. When damaged cells reproduce, they may cause cancer.

- Flaxseed - A great source of dietary fiber, flaxseed can lower the risk of CRC. Flaxseed also contains omega 3 fatty acids, recommended for several health-related issues, from asthma to depression. The seeds can be eaten whole in oatmeal or cooked in meatloaf. Seeds can be ground and used as an egg replacement in recipes. Ground up seeds have more Omega 3 fatty acids available. Whole seeds act more like an insoluble fiber.
- Apples - An apple provides 10% of your daily dietary fiber and vitamin C. Pectin in apples also protects colon cells, according to the AICR, and the fruit contains antioxidants such as quercetin and triterpenoids. According to the AICR, a third of an apple's antioxidants are found in the peel.
- Spinach - All green leafy vegetables contain fiber, which can protect against colorectal cancers, and carotenoids, pigments which some researchers have found fight the growth of some types of cancer cells.
- Walnuts - These nuts have several antioxidant polyphenols, including some that lower blood cholesterol. Nuts are also associated with brain health.
- Tomatoes - This versatile fruit contains lycopene, a phytochemical that has received a lot of attention for its cancer-fighting properties. Lycopene is enhanced when cooked.

<http://theadvocate.com/news/acadiana/12813536-123/food-fighters>