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Title:

Polyp prophylactic properties of polyacetylenes in patients with previous polypectomy

Dansk: Kræftforebyggende effekt af Polyacetylener i gulerødder hos patienter der har fået fjernet et adenom I tyktarmen

In short: Px7

Project members, place of conduction and responsible persons:

The project is led by the Unit for Neoplastic Colorectal Research, Department of Surgery, Odense University Hospital, House of Research, Baagøes Alle, Svendborg Hospital, Svendborg.

Lead: Professor Gunnar Baatrup, same place.

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Abstract:

Background: Carrot cultivars with a high content of falcarinol and falcarindiol have a strong antineoplastic effect in primed rats. The necessary corresponding blood concentration can easily be obtained in humans. High intake of carrots has been shown to reduce bowel cancer in humans in prospective cohort studies, and carotenes have been shown not to have any effect. A prophylactic effect against other cancers in humans especially of the lung and pancreas has also been indicated (1).

Patients who had polyps resected that are considered high risk will be offered a follow up (FU) colonoscopy after 1 year and after 3 years according to national guidelines. At this FU, about 30-40% of them will present with local recurrence or new polyps on colonoscopy.

The study will follow the new national guidelines with the approved acceptable timeframe adjustments, this meaning we will conduct the control colonoscopy at 3 months for piecemeal resection and a full colonoscopy at 1 year for all the patients involved in the study.

More than 90% of bowel cancers arise from adenomas and therefore prevention of adenomas is effective in preventing colorectal cancer.

Method: We aim to include and randomize 400 patients at the four institutions into two groups of equal size. It is expected that 80% of those will comply throughout one year of treatment. The patients are randomized blindly into one group receiving daily 100 ml active carrot juice and one group receiving 100 ml placebo. This amount has been calculated from our experiments in rats to be a sufficient volume as measured by serum concentration. After 1 year, we will register the number and sizes of polyps diagnosed in the 2 groups.

The primary aim is *to investigate for a carrot-medicated inhibition of neoplastic transformation and growth in high risk humans*.

Background:

The polyacetylenes falcarinol and falcarindiol can be found in vegetables, and particularly in certain varieties of carrots. The level of polyacetylenes varies greatly in different carrot cultivars and varieties (2). Preliminary investigations suggest that the content of falcarinol and falcarindiol is higher in the older cultivars of carrots than in the modern, sweeter commercial varieties. The content of falcarinol and falcarindiol of carrots also depends upon exposure to light and temperature during storage (2). Acceptable conditions of storage have been established.

The biological effects of falcarinol and falcarindiol have been studied in almost 30 years at University of Southern Denmark, Department of Surgery, Odense University Hospital and the Department of Food Science, Aarhus University. It has been established that (1, 4-9):

1. Falcarinol and falcarindiol can be purified in a stable form.

2. Falcarinol inhibits the growth of human cancer-cells in vitro, and the effect is enhanced by adding falcarindiol.

3. Freeze dried carrots, purified falcarinol and purified falcarinol and falcarindiol inhibits the formation of adenomas (cancer precursors) in the bowel of rats primed to develop colon cancer with the carcinogenic compound azoxymethane by 30 – 80 %.

4. Falcarinol and falcarindiol inhibits the growth rate of adenomas in the same rats.

5. A serum level comparable to that of the rats can be achieved in human volunteers by eating 200-400 gram of carrots daily corresponding to 100 ml of carrot juice or smoothies. More than 30 cultivars have been grown for 4 different seasons and varieties with a high content has been identified. These include the purple “Night Bird” used in previous studies and a new candidate “Yellowstone”. Night bird is not commercially available any more. The yellow “Yellowstone” is equal in content and will be used in this study.

6. A method for measuring Falcarinol in human blood and other sources such as carrot juice has been developed and published.

7. Conservation methods and storage conditions with no, or very limited loss of active substances has been established.

8. Correlation between oral intake and serum levels and the pharmacokinetics has been determined in healthy volunteers and published.

9. It is known that polyacetylenes has an anti-inflammatory effect and inhibits the Cox receptors and some interleukins such as TNFα, IL-6 and IL1α in humans. One action of polyacetylenes is therefor similar to aspirin (non-selective COX inhibitor) and pharmaceutical COX 2 inhibitors (Celecoxib), which is known to exhibit a

prophylactic effect against the formation of colon cancer in humans. They have also been suggested as adjuvant treatment to patients with colorectal cancer to prevent recurrence.

10. Proteomic analysis have strongly indicated that patients can be divided into 3 groups according to their genomic profile to be high, medium or low in susceptibility to COX2 inhibition indicating a possible road for personalized prevention.

The aspirins are not in general use for cancer prophylactics because it induces stomach- and duodenal ulcers and the selective COX 2 inhibitor is not used mainly because they increase the risk of cardiac failure related mortality. This has been ascribed to suppression of serum prostacyclin. None of these side effects have been described after the intake of carrots, but treatment with purified carotene has been described to increase the risk of cancer development in the prostate. The polyacetylenes from carrots and their interaction with human cancer cells and enzyme systems have been systematically investigated and published during the last 15 years from our study group and others (1, 4-9).

We have conducted 3 studies in rats where we confirmed a statistical significant reduction of neoplastic developments in the forms of both aberrant crypt foci and adenomas; and a reduced growth velocity of these neoplasms (6,8,9). The rats were given both falcarinol and falcarindiol, and the prophylactic effect found in earlier studies on falcarinol only was confirmed and synergistically enhanced to the same level as freeze dried carrots. The reduction of early neoplasms was in the order of 35 % increasing to 80 % for later stages of neoplasms (large adenomas). One of our later studies conformed a dose-response in the azoxymethane induced rats and gave the basis to determine the lowest therapeutic level necessary to achieve a maximal prophylactic effect.

Overall, the available evidence suggests that regular consumption of FaOH/FaDOH rich carrots should have a protective effect on colorectal cancer in humans. The research field is still relatively new and despite the fact that the necessary FaOH/FaDOH concentrations are easily achieved in humans, no randomized clinical human trials has been conducted.

Project description for a human trial on colorectal cancer prophylaxis:

Aim:

Primary aim:

To investigate for a possible inhibitory effect from carrot juice on the recurrence of excised adenomas and, on the formation of metachronous adenomas in patients who are enrolled in a follow up program after resection of high risk colorectal adenomas.

An inhibitory effect of carrot juice will be measured by a combined endpoint of total number of recurrent adenomas multiplied with mean size of recurrent adenomas in the active arm or the placebo group. This difference will be significant if carrots mediate a 20% reduction in both size and numbers.

If the difference in number of polyps is 40 % or more, we will be able to prove this to be significant. If the difference in polyp size is larger than 40 % we will also achieve statistical difference between the 2 groups.

Secondary aim:

Compliance and side effects will be registered through questionnaire and diary and we will identify critical pathways in patient acceptability and compliance of carrot intake from a diary.

Outcome measures

Primary:

- The primary outcome is the number and size of polyps found at the one-year follow up colonoscopy in the treatment arm and in the placebo arm.

Secondary:

- Number of patients with polyps in the two arms
- Polyp number and size in relation to level of compliance to treatment.
- Risk stratification of polyps identified at follow up in each arm.
- Number of polyps with low, medium and high degree of dysplasia and cancer.
- Compliance, side effects and acceptability of treatment.
- User preference of carrot intake across patient profiles and carrot products.

Project organization and primary activities presented as work-packages (WPs)

A network for prevention of colorectal cancer has been established and organized in 2019, supported by DCCC.

The project is anchored in Denmark and will be led by Prof. Baatrup from the Odense University Hospital (OUH) in Odense. The project management will also be handled by the OUH.

Prof. Gunnar Baatrup, Dept. of Surgery at OUH: Clinical trial site Denmark (OUH)

Prof. Anna Martling, Karolinska University Hospital, KUH: Clinical trial site Sweden (KUH)

Prof. Peter Thelin Schmidt, Akademiske Sygehus, Uppsala. Clinical Trials Sweden (UUH)

Ass. Prof Thomas de Lange, Department of Molecular and Clinical Medicine, Sahlgrenska University Hospital (SUH)

Prof. Danielle Wilde, Umeå Inst. of Design, Umeå University, UMU Patient participation and adherence (UMU)Industry partners

Klaus Vestergaard, DanRoots A/S, (DR)

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Jesper Nordall Madsen, Orskov Food (OF)

Martin Jørgensen, Skarø Is A/S (SI)

Project description

WP1. Px7 Clinical trial **(Lead: OUH. Partners: KUH, UUH, UMU, DR, NF, OF)**

Task1.1 Cultivation and quality control of carrots and juice production(Lead: OUH. Partners: DR, NF, OF)

DR will ensure timely production of the necessary amounts of "Yellowstone" carrots. The carrots will subsequently be transported to OF and NF, for production of both the carrot and the placebo juice. The final products will be shipped to the included centers 4 times a year. Other preparatory activities will also be handled in this task.

Task1.2 Quantification of FaOH and FaDOH in the carrot and placebo juice. (Lead:OUH)

Both the carrot and the placebo juices will continuously be analyzed for FaOH/FaDOH contents throughout the study period. Any significant change in the concentration will be compensated.

Task1.3 Preparation of the clinical trial (Lead: OUH. Partners: KUH, UUH, SUH)

The necessary preparations for the clinical trial will be undertaken. This includes obtaining the necessary regulatory and ethical approvals in both Denmark and Sweden, establishing an electronic Case Report Form (eCRF) using the REDCap software, writing trial instructions for staff, developing patient information material and consent forms, creating a randomization system with country stratification, and organize logistics. Finally, we will conduct dry-runs to test the functionality of all the different parts of the study.

- A database will be constructed in RedCap OPEN.
- Instructions for staff will be implemented.
- Approval from ethics committees and data protection agencies in Denmark and Sweden.
- Patient information and consent forms.
- Randomization systems with country stratification
- Dry runs will be performed to test logistics and patient flow.

Task1.4 Clinical trial (Lead: OUH. Partners: KUH, UUH, SUH)

We will conduct a prospective double-blinded randomized controlled trial in 1 Danish and 3 Swedish centers. Participants in the intervention arm will receive a daily treatment with 100mL FaOH/FaDOH-rich carrot juice for 1 year. Participants in the placebo arm will receive a daily treatment with 100 mL of placebo juice for 1 year.

We will include patients who undergo a resection of high-risk colorectal adenomas, who meets the inclusion criteria at the time of their procedure.

WP 2 – Patient compliance (Lead: OUH and UMU)

Task 2.1 – compliance (Lead: OUH and UMU)

Through a close collaboration OUH and UMU will look at ways to keep compliance up for participant.

Task 2.2 – Carrots (Lead: OUH and UMU)

UMU will look at different ways of how to use carrots and also how to make the juice more delicious if there is other ways we can implement carrot in our daily routines.

Methodology

Design of the intervention

The trial will be conducted as a double-blind controlled, randomized study. Patients, who, at colonoscopy, had high-risk adenomas, are randomized in 2 arms. One arm will receive 100 ml of carrot juice with a high concentration of falcarinol and falcarindiol daily for 1 year and the other arm will receive 100 ml of placebo juice daily for 1 year until their follow up full colonoscopy. The placebo juice will be produced from commercially available artificial juice without Falcarinol or Falcarindiol. At the follow up colonoscopy, another standardized report will be fulfilled by the endoscoper, containing information about recurrence, the number of polyps, polyp size and risk stratification (no-, low-, medium, high risk polyps or cancer).

The compliance will be registered through diaries/calendars and patients will be followed through the entire period, regardless of their level of compliance. Patients with compliance drop-outs will be encouraged to reenter and complete with as high a compliance as possible.

Patients will be informed that they will receive a call after 1 month from each appointment, where their questions and concerns will be answered.

After the first colonoscopy, patients will be offered inclusion into the trial. If the resection of the high-risk polyp took place in the first colonoscopy, the patient will call the project nurse if he/she is interested in participating in the study and make an appointment for being enrolled in the project. . If the resection will take place in a specialized unit where a second colonoscopy will be performed for the resection, then they will give their final answer at this appointment.

The patient will collect 8 liters of juice/placebo every 2 months at a visit at the clinic. At this visit, they will be interviewed for compliance, intake of additional carrots/carrot containing products and possible side effects. If the project nurse assesses the patient as non-compliant then he/she will be excluded from the study.

Each participant will have 6 visits and the 4 institutions will in total have 2400 visits, which is approximately 600 visits in two years at each institution. Visits can be organized in weekly group sessions. Compliance diaries and questionnaires will be explained and collected according to written instructions.

Inclusion criteria

1. The patient has adenomas larger than 20 mm in size

2. The patient is willing to accept the treatment and follow-up program for1 year.

3. The patient is capable to understand and follow the instructions. The patient gives written informed consent.

Patients meeting the following **exclusion criteria** will be excluded from the study:

1. Patients allocated to "high-risk" group because of many small polyps (>4).

2. Mental illnesses or suspected significant compliance challenges.

3. Pregnancy.

4. Known allergy to carrots.

Sample size:

Patients seen at the one-year follow up after high risk polyps have 40 % chance of having new polyp/polyps at the colonoscopy. The difference in polyp number found between treatment and control in rats was 40%. The difference in large polyps was 80 % but this is based upon small numbers. The possible effect in humans is unknown. A difference of 10 % or 20 % would be of clinical interest. To test for a difference of 20 % would demand the enrolment of 1248 persons, which is not realistic.

The study is dimensioned to prove a significant difference in number of polyps after 3 years and a significant difference in the combined endpoint (number x size) after 1 year of treatment. The expected effect in number of adenomas in the active and the control arm is a > 20% reduction (corresponding to a 50% relative reduction).

1. The recurrence rate is estimated to 40%
2. The acceptance rate to participate is 55%.
3. The exclusion rate is 20%
4. The total drop-out rate is expected to be 20%.
5. The drop-out patients are estimated to an average 6 months participation.

We assume 80% power and a standard deviation of 5%. Using a two-sided X2-test, a total of 726 patients have to be invited with a minimum of 328 patients to complete the trial. Due to the expected variability of the factors above, we aim to include a total of 400 patients equally to either case or controls. Achieving this number of included patients will require approximately 1.000 possible candidates to be invited. The combined capacity of the included centers is 1.600 eligible patients per year. Therefore, we estimate that the enrollment can be completed within 12 months.

Patient inclusion

The number of participants in the cohort will be 0 at day 1 increasing to 400 at 12 months. After month 12 the number of participants will decrease steadily until month 24 where the last patient is finishing the trial. Information and inclusion will be handled by the endoscopist or a research nurse with GCP certificate.

Patient recruitment:

Patient inclusion is performed at the endoscopic units (Department of Surgery, Odense University Hospital, Södersykehuset, Stockholm, University Hospital, Uppsala, Sahlgrenska Goteborg). All patients undergoing a resection of high-risk adenomas as defined in inclusion criteria at one of the recruiting units will be offered participation if no contraindications are present.

Patient inclusion, flow and randomization procedure:

Two scenarios:

Scenario 1 - Resection at first visit:

Finding and removing high-risk polyp at the current colonoscopy

After performing the colonoscopy, the endoscopist will consider the inclusion and exclusion criteria and if the patient is eligible he/she will be given an oral information about the study (attachment 4 b). All information will be given along with information about the finding from the colonoscopy according to national guidelines in privacy by the endoscopist or the specialized nurse (in a private room with close d doors to ensure patient confidentiality). The patient is informed that he/she has the right to have a person of his own choice to participate. If the person is not there at the moment, the patient can come accompanied after the 48 hour time to think, to a talk at the scheduled location – the information will also be given accordingly to confidentiality guidelines in a private room by an endoscopist or the specialized nurse. The patient will receive written information and informed consent to bring home and will be given at least 48 hours of consideration time before signing it. The patient will call the project nurse if he/she is interested in participating in the study and will not be contacted regarding the clinical study if he/she does not contact us.

If the patient agrees, he/she will come to the facility with informed consent signed and will be instructed by the project nurse and also receive a diary/calendar, questionnaire and 8 liters of juice for 2 months treatment.

Scenario 2 - Resection at second visit:

Finding and not removing high-risk polyp at initial colonoscopy, following a referral to specialized unit for later removal.

At the first colonoscopy polyp (s) are identified that need referral to EMR/ESD. Patients are informed about the project and informed consent and written info are handed out. All information will be given along with information about the finding from the colonoscopy according to national guidelines in privacy by the endoscopist or the specialized nurse (in a private room with close d doors to ensure patient confidentiality).The patient is informed that he/she has the right to have a person of his own choice to

participate.. When they come back to the specialized unit for resection, earliest 48 hours after the first colonoscopy, the patient will bring the informed consent signed if he wants to participate in the study or if he/she has further questions or needs another person to be present at the discussion, the project nurse will answer the questions and furthermore instruct the patients. If the patients agrees entering the study, they will be handed out 8 liters of carrot juice, diary and questionnaire.

For further information about the recruitment scenarios, see attachment “patient flow”.

Common pathway

At the inclusion visit, a compliance diary/calendar will be handed out for registration of compliance and also a basic questionnaire. Patients will be given 2 months juice (8 liters) when included and will be appointed after 2 months to collect another 8 liters of juice in the department. Patients will be informed that they will receive a call after 1 month from each appointment, where their questions and concerns are answered. If the patients need to reschedule the appointment he/she can call at the number that will be written on the information paper or if he/she doesn’t show up, the dedicated staff will contact them on the number they wrote in the questionnaire.

Regarding of the recruitment scenario (1 or 2), in order to follow the national guidelines, patients who have had a piecemeal resection will have an additional control colonoscopy at 3 months.

All patients will undergo a full colonoscopy at one year from the moment of the enrollement After the procedure, information about recurrence, the number of polyps, polyp size and characterization will be registered in the database. Polyp size will be measured with the aid of appropriate instruments, like biopsy forceps and slings.

After completing the study period of 1 year, all patients will enter the standard follow up program.

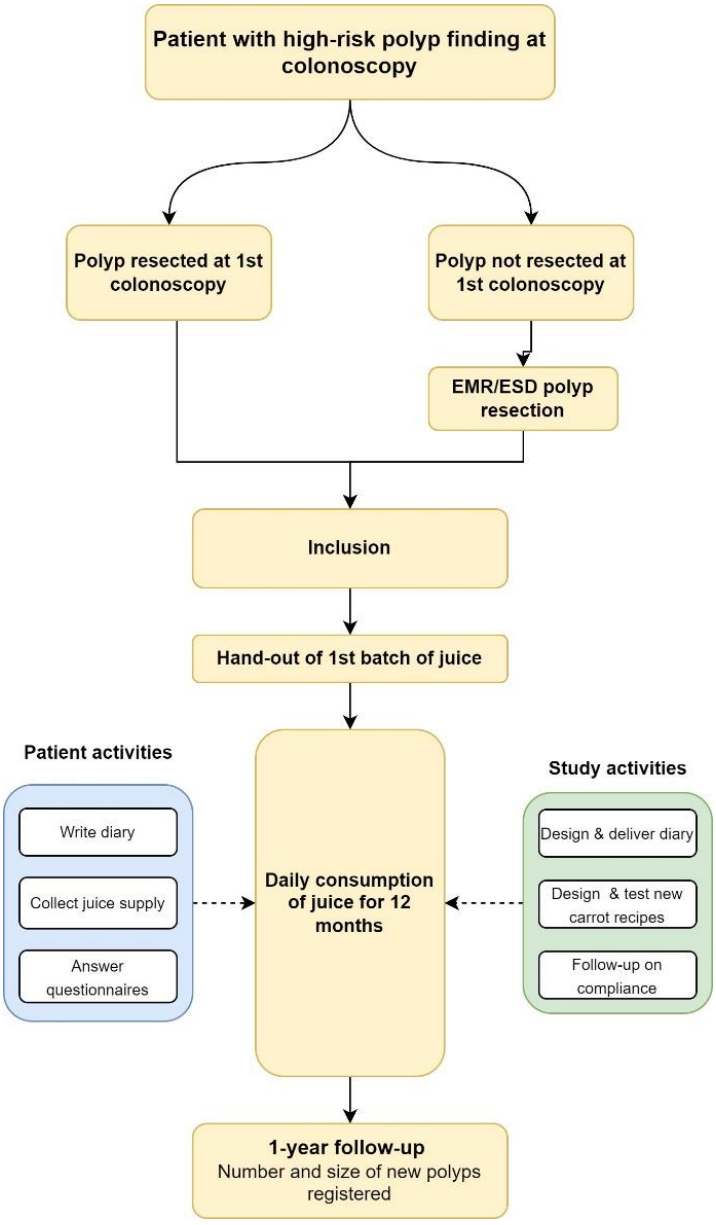
Full compliance is defined as consumption of > 75% of the juice delivered. However, because we do not know the minimal effective dose, all participants will be encouraged to continue the study even if they had drop-outs of juice consumption that lead to a < 75% compliance. In addition, participants with incomplete compliance will be registered and included in the study as a sub-group for separate analysis. But the project nurse will assess the patients every 2 months when they pick up the juice and if almost complete non-compliance is registered, the patient will be excluded from the study.

Randomization: The study is designed as a double-blinded, randomized controlled study. The randomization is stratified by inclusion center, each having its own block of 50/50 distribution between active and placebo arm. Each unit will receive blocks of juice marked A and B for the active juice or either the placebo juice. The randomization key is generated in the RedCap randomizer. The juice producer holds the key for supplementary delivery to each participant center every 6 months. New shipments are delivered, marked with the same randomization letter.

When the last patient has taken the last dose, the code is broken and patient identity and information of active/placebo juice is combined in the database by an independent staff member.

Deviation from standard treatment

The time from adenoma resection to follow-up colonoscopy in case of high-risk adenomas was in Denmark 1 year and for piecemeal resection for 3 months control colonoscopy and after 12 months for full colonoscopy. This has been changed per May 1, 2023 to: for piecemeal resection-at 6 months a control colonoscopy and afterwards a full colonoscopy at 18 months and for en-bloc resection a full colonoscopy at 18 months. In Sweden, the period is 1-3 years depending on the type of high-risk adenomas. In this study piecemeal resection patients are invited at a 3 month control colonoscopy and they are all invited for full colonoscopy after one



year. This means that patients will have an earlier follow up. This regimen is compliant with international guidelines in many European countries.

Risks disadvantages and side effects.

The risks are considered low. Few patients will have a control colonoscopy earlier by 3 months (as was the standard procedure until May 2023). The clinical guidelines for a follow up colonoscopy has been after 1 year in Denmark until May 2023. As European, British and American as well as Swedish guidelines offer a 1-3 year follow up there will be no risk for the patient to have the follow up after 1 year.

Carrot juice are considered health promoting for several reasons, and any toxic dose cannot be obtained with the amounts delivered. Discoloration of skin might be seen I cases who take higher doses than recommended. The placebo juice is produced by commercially available juice and taste additives (ginger). The calories contained in both products might theoretically give a low gain of body weight.

Data collection, management and analysis

Data will be collected after informed consent will be obtained. Patients will be informed that researchers involved in the project will have access to their data and in need (control or inspection purposes), sponsors and regulatory authorities will have access to our database.

The consent provides the responsible researcher, sponsor, investigator, and their representatives, as well as any regulatory authority, direct access to obtain information in the patient's medical records, including electronic records, for the purpose of reviewing information related to the subject's health status that is necessary for the conduct of the research project and for monitoring purposes, including self-monitoring, quality control, and monitoring tasks that they are obligated to perform.

Data collection will be performed by dedicated research staff. Data will be collected and entered into the electronic database REDCap via OPEN at OUH. We will enter data from the questionnaire, patient journal, pathology answer etc.

Information collected from patient files and questionnaires:

From the patient file: Quality and technical details of both colonoscopy, allergies, former colonoscopies and polypectomies and the pathology report on adenomas resected. Only data necessary to answer the described aims will be collected.

We will not need to give patient information to others to recruit patients. The patients will be invited to participate if they have a polyp bigger than 20 mm regardless of other information from the patient journal which we will not access at this timeline. Patient information will not be collected at the inclusion but will be accessed by research responsible and entered into a RedCap database after the patient will be already included in the project. Only project members have access to data and data will be destroyed after analysis. The project will be registered in the Data Protection Agency. The data protection law and regulations will be obeyed including the chapter V.

Data obtained in Sweden will be entered into the Danish RedCap database in OPEN directly after a data sharing agreement has been lawfully obtained between the sites. After the completion of the database all data will be pseudoananomized. Data will be destroyed after publication of the results from the 3-year colonoscopy, or – if scientifically useful, prolongation until the 5-year colonoscopy will be applied for.

Patient information from patient journals

To investigate if carrot juice has an effect on polyps we need some information from the patient journal. Research responsible will get this information from the patient journals and entered into the RedCap database.

Patient journal information:

- Pathology results
- Endoscopy results
- Previous cancers
- Past colonoscopies
- Name
- Age
- Gender
- Height
- Weight
- Social Security Number (CPR in Danish context)

We require the information to analyze the identified polyps to compare them with the control follow-up. Age, gender, height, and weight will be used for comparisons and correlations. Name and CPR (Central Person Register - Danish identification number) are needed for patient registration for further anonymization.

Data retention, storage, destruction and publication

All data will be stored in the electronic database REDCap via OPEN on password-protected computers. All electronic data will be backed up and stored electronically in password secured computers. All paper data will be archived and stored in a locked cabinet in the Research Office of the Department of Surgery, OUH. Data retrieved from EPJ is transferred to the RedCap database directly. Data is stored securely in the RedCap database for 5 years (until 31 December 2028), after which will either be destroyed or transferred to the National Archives.

Additionally, we plan to publish the findings in a peer-reviewed journal. Participant anonymity and confidentiality will be preserved as only aggregated findings will be presented or reported. In case of data breach, the incident will be reported to Datatilsynet and the affected participants will be informed.

The Data Protection Regulation and the Data Protection Act are complied. The project is registered with the Data Protection Agency before the start of the project.

Product – carrot juice and placebo

The cultivation of "Yellowstone" carrots will be conducted by DanRoots A/S.DanRoots, Organic Vegetables, Bjerringbro, Denmark. For each kg of carrots, 800 ml of juice can be extracted. There will be some waist by distributing the juice and placebo to four different locations. We have ordered 7.5 tons carrots for delivery November 1th 2023 and 7,5 tons carrots by November 1th 2024.

Juice is produced and taste corrected by Orskov Food, Denmark in collaboration with Naturfrisk, Ørbæk. The test is corrected to prevent enabling differentiation between carrot juice and placebo.

Analysis of carrot juice for falcarinol and falcarindiol content will be done at random from 10 samples leaving the factory and 10 samples collected after 30 days storage at participant's homes for each batch.

All laboratory investigations are performed at the Dept. of Biochemestry, Svendborg Hospital.

Ethics:

Participation is voluntary with no economic compensation, and the patients are informed orally and in writing according to the information accepted by the ethics committee. They will be given at least 48 hours to consider participation. As the study is structured as a two-armed trial wherein one group will receive active carrot juice while the other will receive a placebo drink, there is no guarantee of patient benefit from participation. The effectiveness of the active carrot juice is not assured, and this is the principal focus of investigation within the study. However, patients are invited to participate due to the potential of specific carrot compounds and their hypothesized capacity to reduce cancer risk.

There are no known side effects to the consumption of carrot juice in the used amount. The lowest toxic dose giving side effects is > 20 times higher than the one offered (10). Meta analyses have demonstrated that a high consumption of carrots is correlated to a reduced mortality risk (1,5). The juice and placebo has been used in an earlier trial with the permission from the Ethics committee (your journal number 21/60480) with no observed side effects.

The deviation from standard follow-up periods is believed to cause no, or very little additional risk to patients. Some Swedish patients are investigated 1-2 years earlier and some Danish patients 3 to 6 months earlier.

It is our judgement that the potential gain by producing evidence for at effective prophylaxis against colorectal neoplasia and likely cancer by large outweighs the theoretical side effects and disadvantages of the trial.

Approval from the ethical committee has not yet been obtained but is considered to cause no problem. The National Danish Drugs Administration has been consulted and the trial is not considered to be a drug-trial and is not under the GCP regulations and can therefore be initiated without their approval. The project is registered internally to the Region of Southern Denmark (intern fortegnelse over forskningsprojekter) .

Patients are covered by the Patient Insurance (patientforsikringen) in Denmark and the “patientförsäkring” in Sweden.

Economy:

The study is investigator initiated. Our commercial partners have provided carrots and juice for free and at reduced prizes. No money has been payed by commercial companies. The foundation: Sygeforsikringen “danmark” has donated 5 mio dkk to the condition of the trial. (budget attached). No project member have personal benefit besides their regular salary by the participation and no economic interests in any of the commercial partner companies. The grant is managed by “Forskerservice”. The hospital economy department at Odense University Hospital and the account is subject to public revision. The study hasn’t received any other funding.

There will be no compensation to trial participants.

Time schedule:

The clinical studies:

Protocol for the Px7 trial will be finished before October 1´th 2023, including approval from the ethical committee and the data protection agency.

Database and electronic randomization algorithm will be ready before October 1´th 2023

Experiments with placebo juice ended before October 2023. For effective inactivation and taste adjustments.

Planting carrots will be ordered in March 2023 (done) and harvested in October 2023 and October 2024

Contract on juice production before July 2023 (done)

Questionnaires for patients will be finished before December 2023.

Inclusion of patients into the px7 trial will await the 2023 carrot harvest. It can be initiated November 2023. Inclusion will take 12 month, and observation until follow up colonoscopy will be ended January 2026.

Publications will be produced before January 2027.

Publication plan:

The protocol will be published in Clinical Trials.com or a similar journal.

The results will be published at clinicaltrials.gov or clinicaltrialregister.eu, the results will be published regardless of they are positive, negative or inconclusive for the study.

The main paper and all spin off papers will be published in international open access journals. Vancouver rules will be followed when deciding authors. Both positive and negative results will be published.

The communication co-worker Lene von Fintel Sostack, The Surgical research Unit, OUH on the project will timely inform the press and other public actors to achieve maximal national coverage for the general population.

Budget:

Attached as a separate file.

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