Chemoprevention for Gastrointestinal cancer IAGH Symposium Aban 1404

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A 77% increase in World cancer annual rate by 2050

- The current global statistics for the year 2025 indicate that there were almost 22 million new cases of cancer and close to 11 million cancer deaths.
- Demographics-based predictions indicate that the annual number of new cases of cancer will reach 35 million by 2050, a 77% increase from the 2022 level.

Escalation of targeted cancer control

- The need for a global escalation of targeted cancer control measures.
- Investments in prevention, including the targeting of key risk factors for cancer including:

➢ **Smoking Tocacco , Opium and Alcohol**

➢ **Overweight and obesity**

➢ **Infections**

❑Can avert millions of future cancer diagnoses and save many lives worldwide, bringing huge economic as well as societal dividends to countries over the forthcoming decades

Prevalence of Key risk factors of cancer in Iran based on data from Persian Cohort

- Tobacco use:%14

(cigarettes and water pipe)

- Opium use: 10%
- Alcohol use :10%
- Obesity: 30% in female 18% in male
- H.Pylori infection: 50%

Persian Cohort profile Am J Epidemiol. 2018 Apr 1;187(4):647-655.

GI cancers remain a major cause of cancer-associated mortality.

- Despite substantial progress in screening, early diagnosis, and the development of noninvasive technology, gastrointestinal (GI) cancer remains a major cause of cancer-associated mortality.

- Chemoprevention is thought to be a realistic approach for reducing the global burden of GI cancer, and efforts have been made to search for

Number and ASR (per 100,000) of top 5 cancers in Iran in 2018 _ Total population

Organ	Number	ASR
Breast (Female)	19,263	44.42
Prostate	8,350	22.06
Colorectal	13,363	16.57
Skin (non-melanoma)	12,291	15.50
Stomach	11,062	13.70

GI Cancers In Iran

EC,GC,CRC,PC

- Constitute 30% of Cancer death in Iran.
- Colorectal cancer is the 3rd common cancer in Iran and constitute **16.5%** of all cancer death in the country.
- Gastric cancer:is the 5th common cancer in Iran and constitute **11%** of all cancer death in the country.
- **Oesophageal cancer is the 11th cancer and constitute 5% of all cancer death in the country**

Diet the most powerful cancer risk factor

- "Diet is one of the most powerful cancer risk factors. Poor nutrition contributes to inflammation, metabolic dysfunction, and DNA damage.
- Up to 50% of cancers could be prevented with healthier eating patterns."
- The World Cancer Research Fund has also asserted that 'between 30 and 50% of cancers' are preventable through healthier lifestyle choices and avoiding carcinogen exposure.



Dietary Interventions. A diet rich in :

- Fresh fruits.
- Vegetables.
- whole-grain cereals
- Green tea

What is the etiology of very high rate of ESCC in NE Golestan?



Mahboubi E, et al. Br. J. Cancer, 28: 197-214, 1973

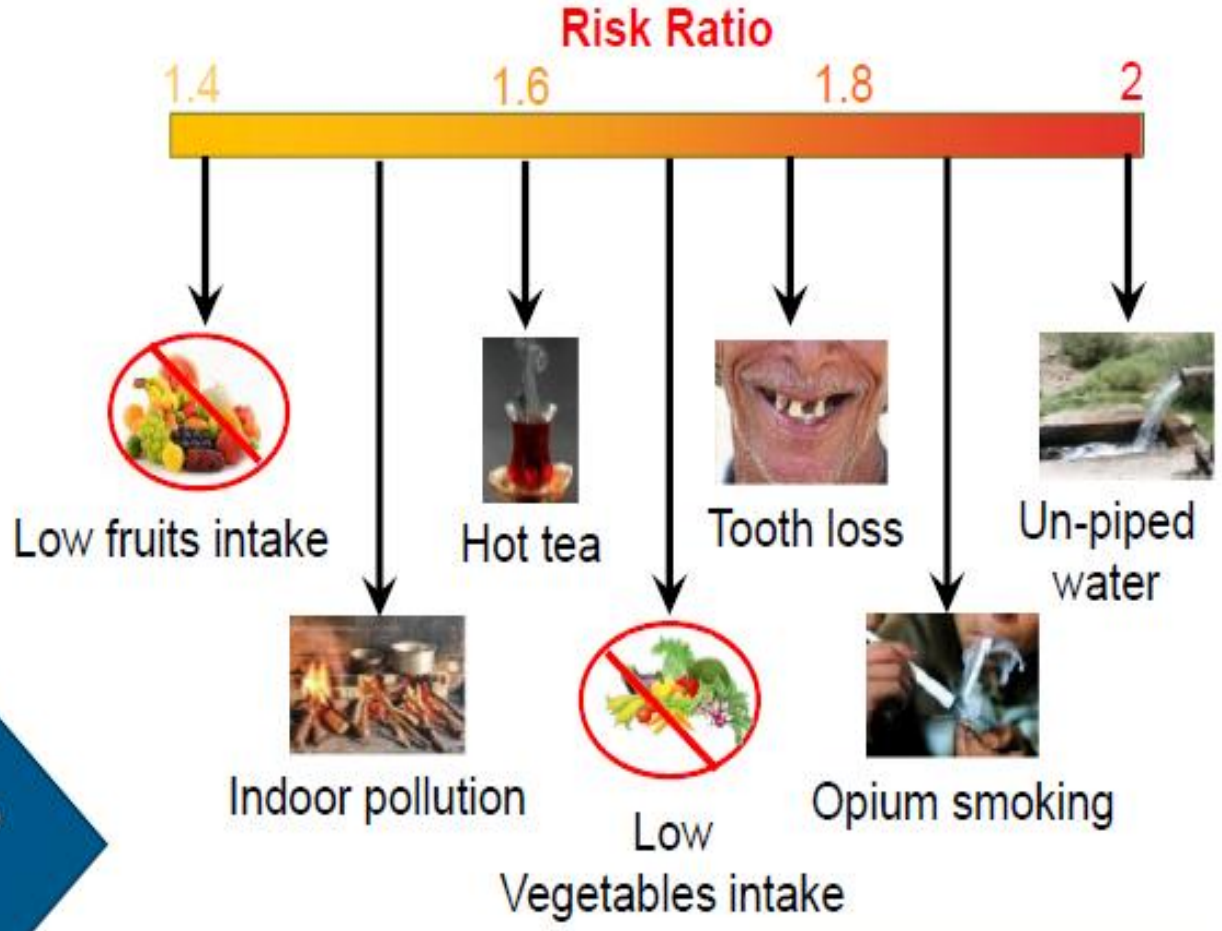
76% of ESCC are due to these 7 risk factors

Golestan Cohort Study



- Designed in North-East Iran to study esophageal cancer
- > 50,000 participants
- > 10 years of follow-up

76% of esophageal cancer cases are attributable to combined exposures to these risk factors



Gastroenterology 2019

There is no association between dietary vitamin D and the risk of GC.

European Journal of Nutrition (2025) 64:269
https://doi.org/10.1007/s00394-025-03768-w

ORIGINAL CONTRIBUTION

Dietary vitamin D and gastric cancer risk within the stomach cancer pooling (stop) project

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Abstract

Purpose The evidence regarding the role of vitamin D on gastric cancer (GC) is controversial. Within the Stomach cancer Pooling (StoP) Project, a global consortium of epidemiological studies on GC, we aimed to evaluate the relationship between dietary vitamin D and GC risk.

Methods Five case–control studies were included in the analysis, accounting for 1875 cases and 5899 controls. Odds ratios (OR) of GC and the corresponding 95% confidence intervals (CI) for tertiles of vitamin D intake were computed using logistic regression models adjusted for relevant confounders, including energy intake. The pooled ORs were computed using random-effect models.

Results The pooled OR of GC for the highest compared to the lowest tertile of vitamin D intake was 1.06 (95% CI 0.80–1.39), with a p for heterogeneity of 0.019. No significant association was found across strata of sex, age, socioeconomic status, smoking status, alcohol intake, and vegetable and fruit consumption.

Conclusions Our pooled analysis indicates that there is no association between dietary vitamin D and the risk of GC.

Fish and canned fish intake are not associated with gastric cancer risk.

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Fish consumption and gastric cancer within the Stomach cancer Pooling (StoP) Project

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Vitamin C is inversely associated with GC, with a potentially beneficial effect also for intakes above the currently recommended daily intake

Gastric Cancer (2024) 27:461–472
https://doi.org/10.1007/s10120-024-01476-8

ORIGINAL ARTICLE

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Dietary intake of vitamin C and gastric cancer: a pooled analysis within the Stomach cancer Pooling (StoP) Project

Michele Sassano[1] · Monireh Sadat Seyyedsalehi[1] · Giulia Collatuzzo[1] · Claudio Pelucchi[2] · Rossella Bonzi[2] · Monica Ferraroni[2] · Domenico Palli[3] · Guo-Pei Yu[4] · Zuo-Feng Zhang[5] · Lizbeth López-Carrillo[6] · Nuno Lunet[7,8,9] · Samantha Morais[7,8,9] · David Zaridze[10] · Dmitry Maximovich[10] · Vicente Martín[11,12] · Gemma Castano-Vinyals[11,13,14,15] · Jesús Vioque[11,16] · Sandra González-Palacios[11,16] · Mary H. Ward[17] · Reza Malekzadeh[18] · Mohammadreza Pakseresht[18,19,20] · Raul Ulises Hernández-Ramirez[21] · Malaquias López-Cervantes[22] · Eva Negri[1,2] · Federica Turati[2] · Charles S. Rabkin[17] · Shoichiro Tsugane[23,24] · Akihisa Hidaka[25,26] · Areti Lagiou[27] · Pagona Lagiou[28,29] · M. Constanza Camargo[17] · Maria Paula Curado[30] · Stefania Boccia[31,32] · Carlo La Vecchia[2] · Paolo Boffetta[1,33,34]

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Abstract

Background Previous studies suggest that dietary vitamin C is inversely associated with gastric cancer (GC), but most of them did not consider intake of fruit and vegetables. Thus, we aimed to evaluate this association within the Stomach cancer Pooling (StoP) Project, a consortium of epidemiological studies on GC.

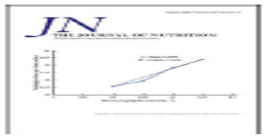
Methods Fourteen case–control studies were included in the analysis (5362 cases, 11,497 controls). We estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between dietary intake of vitamin C and

In the GCS, with refined grains as the main source of plant protein intake has a positive association with GI cancer:Journal of Nutrition 2025

The Journal of Nutrition 155 (2025) 3479–3495

THE JOURNAL OF NUTRITION

journal homepage: https://jn.nutrition.org/



Nutrition and Disease

Dietary Intake of Animal and Plant Proteins and Risk of Gastrointestinal Cancer Mortality: Results from the Golestan Cohort Study

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A B S T R A C T

Background: Gastrointestinal (GI) cancers account for a significant global cancer burden, but the link between intake of proteins from different sources and GI cancer mortality is unclear.

Objectives: This study examined associations between the percentage of energy received from animal protein intake (API) and plant protein intake (PPI), and mortality from esophageal (EC), gastric (GC), colorectal (CRC), and pancreatic (PC) cancers in 42,323 participants of the Golestan Cohort Study (GCS).

Methods: Using data from a baseline food frequency questionnaire, hazard ratios (HRs) were estimated through Cox models, including isocaloric substitution analyses of API and PPI.

Results: During 13.4 y of follow-up, 676 deaths from GI cancer occurred. We found no association between API and GI cancer mortality [$HR_{Q5\ vs\ Q1} = 1.023$; 95% confidence interval (CI): 0.626, 1.673; $P_{for\ trend} = 0.976$], and a positive association between PPI and overall GI cancer mortality ($HR_{Q5\ vs\ Q1} = 2.635$; 95% CI: 1.368, 5.074; $P_{for\ trend} = 0.005$). We identified no association between API and EC mortality ($HR_{Q5\ vs\ Q1} = 0.711$; 95% CI: 0.377, 1.746; $P_{for\ trend} = 0.058$), and a positive association between PPI and EC mortality ($HR_{Q5\ vs\ Q1} = 5.226$; 95% CI: 1.888, 14.459; $P_{for\ trend} = 0.001$). BMI and wealth score modified some of these associations. There was no association between API or PPI and GC, CRC, or PC mortality. We observed a decreasing trend in percentage of energy received from fish protein ($HR_{Q5\ vs\ Q1} = 0.766$; 95% CI: 0.585, 1.004; $P_{for\ trend} = 0.038$) and legume protein ($HR_{Q5\ vs\ Q1} = 0.760$; 95% CI: 0.588, 0.982; $P_{for\ trend} = 0.042$) related to GI cancer mortality. In contrast, refined grains protein showed an increasing trend ($HR_{Q5\ vs\ Q1} = 1.472$; 95% CI: 1.023, 2.117; $P_{for\ trend} = 0.027$).

Development of a Digestive Cancer Risk Score Based on Nutritional Predictors: A Risk Prediction Model in the Golestan Cohort Study

Consumption of plant-based foods items including legumes, nuts (as a part of seafood-plant proteins), and soy had protective role in the incidence of gastrointestinal cancers



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Development of a Digestive Cancer Risk Score Based on Nutritional Predictors: A Risk Prediction Model in the Golestan Cohort Study

Masoumeh Jabbari[a], Meisam Barati[b], Ali Kalhori[c], Hassan Eini-Zinab[a], Farid Zayeri[d], Hossein Poustchi[e], Akram Pourshams[f], Azita Hekmatdoost[g] and Reza Malekzadeh[f]

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ABSTRACT

This study aimed to develop a non-laboratory simple and useful scoring system to predict risk of incident digestive cancers within the healthcare and clinical framework in Iranian population. The present study was conducted on the collected data from the Golestan Cohort Study. A total of 49,173 participants, aged 37-80 years, were recruited from Gonbad City and 326 rural villages and were followed from 2004 to 2021 in Iran. A non-laboratory model for prediction of the 15-year risk of digestive cancers by means of dietary predictors and formulating a simple and useful scoring system in Iranian population was done in this study. A total of 43550 participants (25249 women and 18301 men) were included in the final analysis. The model's discrimination and calibration were assessed by concordance statistic (C-statistic) and calibration plot, respectively. The model had an acceptable discrimination in both derivation (C-statistic: 0.76) and validation (C-statistic: 0.70) samples ($p<0.001$). Also, the calibration of model in derivation and validation datasets was 0.88 and 0.91, respectively. As an assessment tool, the established simple and practical nutritional risk score is suitable for motivating at-risk individuals to change lifestyles and dietary patterns to reduce future risks and prevent health problems.

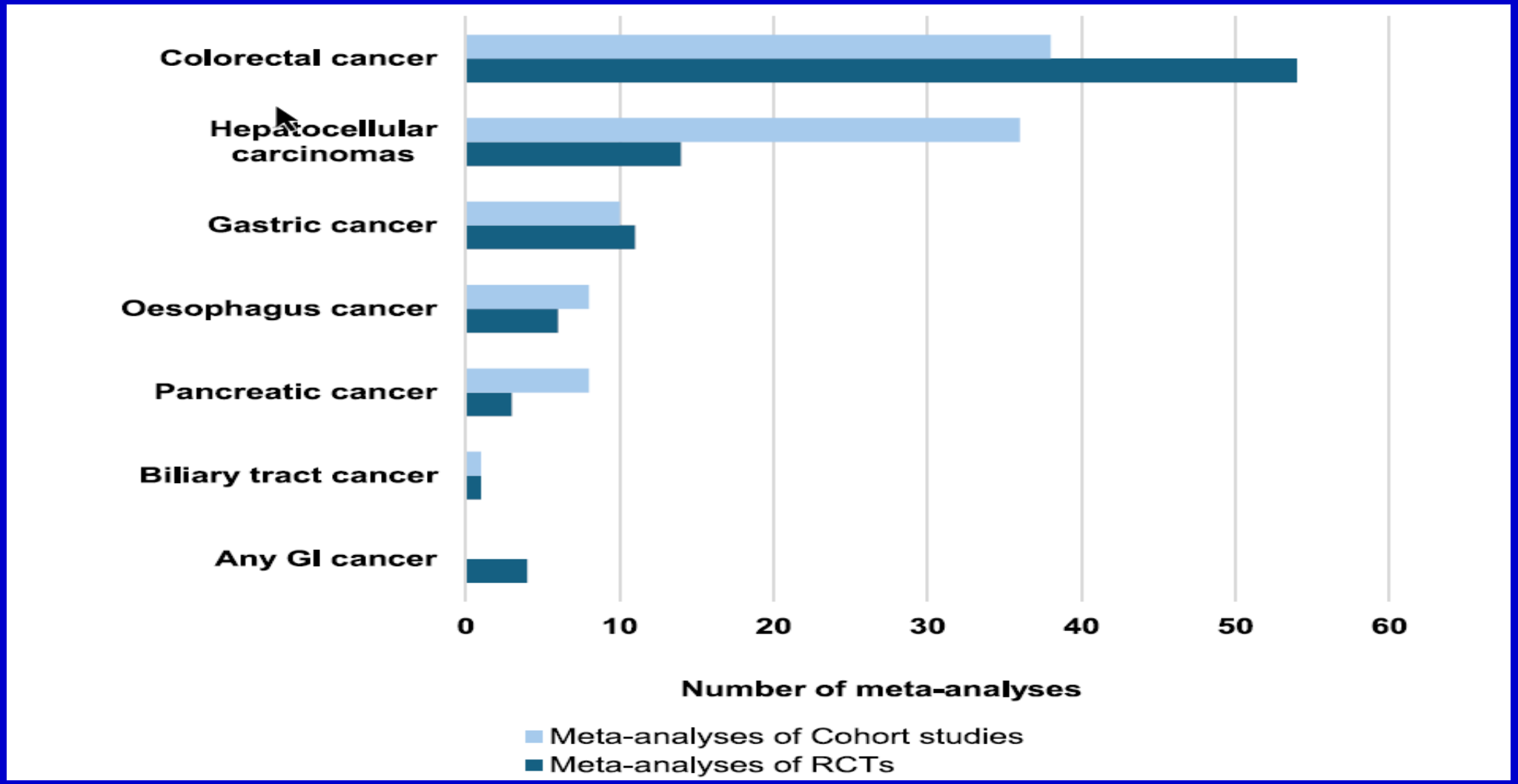
ARTICLE HISTORY
Received 9 July 2024
Accepted 25 February 2025

Chemoprevention is thought to be a realistic approach for reducing the GI cancer

- Targeting Carcinogenesis Mechanisms: Researchers are focusing on understanding factors contributing to GI carcinogenesis, such as chronic inflammation and DNA repair, to develop more targeted preventive agents.

- High-Risk Populations: More research, including long-term randomized controlled trials, is needed to establish the efficacy and safety of chemopreventive agents in populations with a higher risk of specific GI cancers.

Meta-analyses investigating different (GI) cancers chemoprevention in published literature



Conclusions of Meta-analysis on preventive effect of chemopreventive agents

- Overall, the association between several chemopreventive agents (CPAs) and GI cancers has been extensively studied, but only a few associations with CPAs targeting well-established risk factors are graded as good-quality evidence.

- Few CPA approaches, including the use of **aspirin, metformin, and statins,** have demonstrated promising effects in reducing the risk of several GI cancers.

Chronic inflammation inducing genomic instability and telomere shortening affecting polyamine metabolism and DNA repair

- Phytoceuticals,in plant-based diet have also sparked hope for the chemoprevention of GI cancer.
- To perform successful searches of chemopreventive agents for GI cancer, it is of the utmost importance to understand the factors contributing to GI carcinogenesis.

Chemoprevention for GI and liver cancer

- Using natural or synthetic agents to reverse or suppress the early stages of cancer development.
- **Aspirin** which can prevent recurrence of <colorectal cancer (CRC) adenomas, and **Metformin**, which has also shown benefits for CRC prevention.
- Helicobacter pylori eradication is a key strategy for preventing gastric cancer.
- Research is ongoing to identify new agents and optimize combined strategies for more effective and well-tolerated cancer prevention.

Promising Agents and Strategies

- **Aspirin** : Daily use of aspirin has shown promise in preventing adenoma recurrence, particularly in certain high-risk populations.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** are also being investigated, although they can carry significant side effects.
- **Metformin:** This first-line diabetes medication has demonstrated safety and effectiveness in preventing adenoma recurrence in some studies.
- **Combining agents: A**spirin and metformin or Aspirin and statin
- **Helicobacter pylori (H. pylori) Eradication**: For gastric cancer prevention, eradicating H. pylori infection is a significant strategy, as it addresses a known precursor to gastric adenocarcinoma.
- Suppress acid reflux by **proton pump inhibitors**

Chemoprevention should include drug which is :

- Well-tolerated with no side effect
- Minimal side effects, given the long-term administration required.
- Affordable: The agent's cost should not be a barrier to widespread use.
- Easy to administer: The dosing schedule should be convenient.

Aspirin

- Case–control studies and prospective cohort studies showed that aspirin may reduce the risk of premalignant colorectal adenoma and colorectal cancer.

- Data from randomized trials comparing aspirin and placebo with regard to the primary end points or secondary end points of colorectal adenoma and colorectal cancer support epidemiologic data

Best estimates of incidence and mortality are shown in cohort and RCT studies

Condition	Incidence Estimated Risk Ratio	Mortality Estimated Risk Ratio
Myocardial infarction	0.82	0.95
Stroke	0.95	1.21
Colorectal cancer	0.65	0.60
Oesophageal cancer	0.70	0.50
Gastric cancer	0.70	0.65
Lung cancer	0.95	0.85
Prostate cancer	0.90	0.85
Breast cancer	0.90	0.95

Colorectal cancer is the third most common

- Colorectal cancer is the **third most common cancer worldwide**.
- Although 80% of patients with colorectal cancer do not have evident distant metastases at the time of diagnosis, disease **recurrence occurs in 30 to 40%** of patients despite standard treatment.
- Postoperative adjuvant chemotherapy is the standard of care for stage III colon cancer and discretionary for stage II colon cancer.
- The use of multimodal treatment before surgery (as neoadjuvant therapy), during surgery (as bridging therapy), or after surgery (as adjuvant therapy) is the standard of care for both stage II and III rectal cancer.

Aspirin for the primary prevention of colorectal cancer

- In 2016, the U.S. Preventive Services Task Force recommended low-dose aspirin for the primary prevention of colorectal cancer and cardiovascular disease in adults who are 50 to 59 years of age and have a 10-year cardiovascular disease risk of at least 10%.

- The guidance was revised in 2022 because the preventive effects of aspirin were unclear, on the basis of the results of simulation modeling and data from the ASPREE

Aspirin lowers the incidence of adenomas and CRC in high-risk patients.

- Post-diagnosis aspirin treatment improves disease-free survival .
- After three years of follow-up, the HRs for TTR comparing aspirin to placebo were 0.49 (95% CI; 0.24-0.98; p=0.044) in Group A and 0.42 (95% CI; 0.21-0.83; p=0.013) in Group B. For DFS,

Aspirin reduce risk of CRC recurrence

- Multiple observational studies showed that aspirin was associated with a reduced risk of recurrence and improved survival in patients with colorectal cancer.
- However, these observations were not confirmed in a randomized trial of aspirin involving patients with colorectal cancer who were not selected on the basis of a tumor biomarker

Mechanisms for Aspirin’s Role in Cancer Prevention

Liesenfeld B. Journal of Cancer Epidemiology, Biomarkers, and Prevention

OCTOBER 2015

This work was supported by the National Institute of Health, Huntsman Cancer Foundation, and funding from the German Cancer Research Center.

Aspirin and the Risk of Colorectal Cancer NEJM 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2007 VOL. 356 NO. 21

Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of COX-2

Andrew T. Chan, M.D., M.P.H., Shuji Ogino, M.D., Ph.D., and Charles S. Fuchs, M.D., M.P.H.

ABSTRACT

BACKGROUND

Regular use of aspirin reduces the risk of a colorectal neoplasm, but the mechanism by which aspirin affects carcinogenesis in the colon is not well understood.

METHODS

We estimated cyclooxygenase-2 (COX-2) expression by immunohistochemical assay of sections from paraffin-embedded colorectal-cancer specimens from two large cohorts of participants who provided data on aspirin use from a questionnaire every 2 years. We applied Cox regression to a competing-risks analysis to compare the effects of aspirin use on the relative risk of colorectal cancer in relation to the expression of

From the Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School (A.T.C.); the Department of Pathology, Brigham and Women's Hospital and Harvard Medical School (S.O.); the Department of Medical Oncology, Dana–Farber Cancer Institute (S.O., C.S.F.); and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (A.T.C., C.S.F.) — all in Boston. Address reprint requests to Dr. Chan at the Gastrointesti-

Reduction of cox 2 expression

- Regular use of aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2.

Andrew T. N Engl J Med 2007;356:2131-42

Mechanism of cancer preventive effect of Aspirin

- Aspirin down-regulates COX-2, leading to the inhibition of activating mutations in the phosphatidylinositol 3-kinase signaling pathway, which occur in up to 50% of colorectal cancers.
- An observational study showed that the association between aspirin and survival among patients with PIK3CA-mutated cancer differed from that among patients with PIK3CA wild-type cancers.
- This finding provided the rationale for the ALASCCA (Adjuvant Low-Dose Aspirin in Colorectal Cancer) trial, the results of which are reported by Martling et al.8 in this issue of the Journal.

Result of Aspirin Studies

- Suggested that low dose aspirin use is associated with moderate level of lower risk of esophageal cancer and gastric cancer.

- Impact: With the current disease burden of esophageal and gastric cancers in East Asia, low dose aspirin use may play a role in mitigating risk of these cancers

ALASCCA trial: Aspirin reduced the risk for CRC recurrence

- ALASCCA trial— conducted across centers in Sweden, Denmark, Finland, and Norway — assessed patients with stage I-III rectal cancer or stage II-III colon cancer.
- It focused on a subset of patients with an **oncogenic abnormality called PIK3CA(** phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha).
- PIK3CA occurs in approximately a third of colon cancers and is associated with significant chemotherapy resistance and a higher rate of disease progression.

Aspirin dramatically reduced the risk for time to recurrence by nearly 50% at 3 years

- Of the included patients, 1103 (37%) had alterations in the PIK3CA pathway.
- Researchers randomized patients to receive either 160 mg of aspirin or placebo daily for 3years, starting within 3 months of surgery.
- **Among patients with PIK3CA mutations**, aspirin dramatically reduced the risk for time to recurrence by nearly 50% at 3 years (P 10/5/25, 8:24 PM) These Two Simple Interventions May Cut CRC Recurrence Risk
- . Adverse events associated with aspirin were minimal, including one case each of gastrointestinal bleeding, hematoma, and allergic reaction.

For Aspirin you may check their PIK3CA mutation status

- For aspirin, patients should work with their oncologist to determine their PIK3CA mutation status, as this subgroup appears tobenefi t the most.

Aspirin play A key role in interrupting multiple pathways that are linked to cancer development.”

- We now have evidence that other pathways are involved, especially at lower aspirin doses.
- studies suggest that aspirin is playing a key role in interrupting multiple pathways that are linked to cancer development.”
- A reduction in **2-hydroxyglutarate** may identify a new mechanism for aspirin in cancer prevention.”

Aspirin chemoprevention

- Several studies have shown that regular use of aspirin for >10 year reduces the risk of a colorectal neoplasm

- About 70% of CRC show moderate to strong over expression of COX-2

Andrew T. N Engl J Med 2007;356:2131-42

Aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2

- The ASR for CRC that overexpressed COX-2 was 37 per 100,000 person-years among regular aspirin users, as compared with 56 per 100,000 person-years among those who did not use aspirin regularly.

- The ASR for CRC with weak or absent COX-2 expression was 27 per 100,000 person-years among regular aspirin users, as compared with 28 per 100,000 person-years among nonregular aspirin users

Decrease in risk of other Cancer by low dose Aspirin use

- Observational studies suggest that aspirin reduces the risk for several other cancers including:

- **Esophageal.**
- **Gastric.**
- **Biliary**
- **Prostate**
- **Lung,**
- **Breast cancer**

Best estimates of incidence and mortality with low dose aspirin

Condition	Incidence Estimated Risk Ratio	Mortality Estimated Risk Ratio
Myocardial infarction	0.82	0.95
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Breast cancer	0.90	0.95

Dr Choi team From the Center for Gastric Cancer Research Institute National Cancer Center, Goyang, South Korea.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Family History of Gastric Cancer and *Helicobacter pylori* Treatment

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ABSTRACT

BACKGROUND

Helicobacter pylori infection and a family history of gastric cancer are the main risk factors for gastric cancer. Whether treatment to eradicate *H. pylori* can reduce the risk of gastric cancer in persons with a family history of gastric cancer in first-degree relatives is unknown.

METHODS

In this single-center, double-blind, placebo-controlled trial, we screened 3100 first-degree relatives of patients with gastric cancer. We randomly assigned 1838 participants with *H. pylori* infection to receive either eradication therapy (lansoprazole [30 mg], amoxicillin [1000 mg], and clarithromycin [500 mg], each taken twice daily for 7 days) or placebo. The primary outcome was development of gastric cancer. A prespecified secondary outcome was development of gastric cancer according to *H. pylori* eradication status, assessed during the follow-up period.

RESULTS

A total of 1676 participants were included in the modified intention-to-treat population for the analysis of the primary outcome (832 in the treatment group and 844 in the placebo group). During a median follow-up of 9.2 years, gastric cancer developed in 10 participants (1.2%) in the treatment group and in 23 (2.7%) in the placebo group (hazard ratio, 0.45; 95% confidence interval [CI], 0.21 to 0.94; P=0.03 by log-rank test). Among the 10 participants in the treatment group in whom gastric cancer developed, 5 (50.0%) had persistent *H. pylori* infection. Gastric cancer developed in 0.8% of participants (5 of 608) in whom *H. pylori* infection

From the Center for Gastric Cancer (I.J.C., C.G.K., J.Y.L., Y.-I.K., M.-C.K.), the Division of Cancer Epidemiology and Management, Research Institute (I.J.C., Y.-I.K., B.P., J.J.), and the Biostatistics Collaboration Team, Research Core Center, Research Institute (B.P.) — all at the National Cancer Center, Goyang, South Korea. Address reprint requests to Dr. Choi at the Center for Gastric Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi, 10408, South Korea, or at cij1224@ncc.re.kr.

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Prevention of Gastric Cancer

- **H.Pylori Eradication**
- **Long-term aspirin** use seems to have the largest potential effect on the general population on cancer incidence and mortality overall, especially GI cancers. Helicobacter pylori eradication reduces the risk for gastric cancer and is advocated regardless of the symptoms and stage of disease.
- Metformin and statins are promising in cancer prevention in patients with type 2 diabetes.
- Vitamin D supplementation is promising in the prevention of colorectal adenoma recurrence.

Metformin

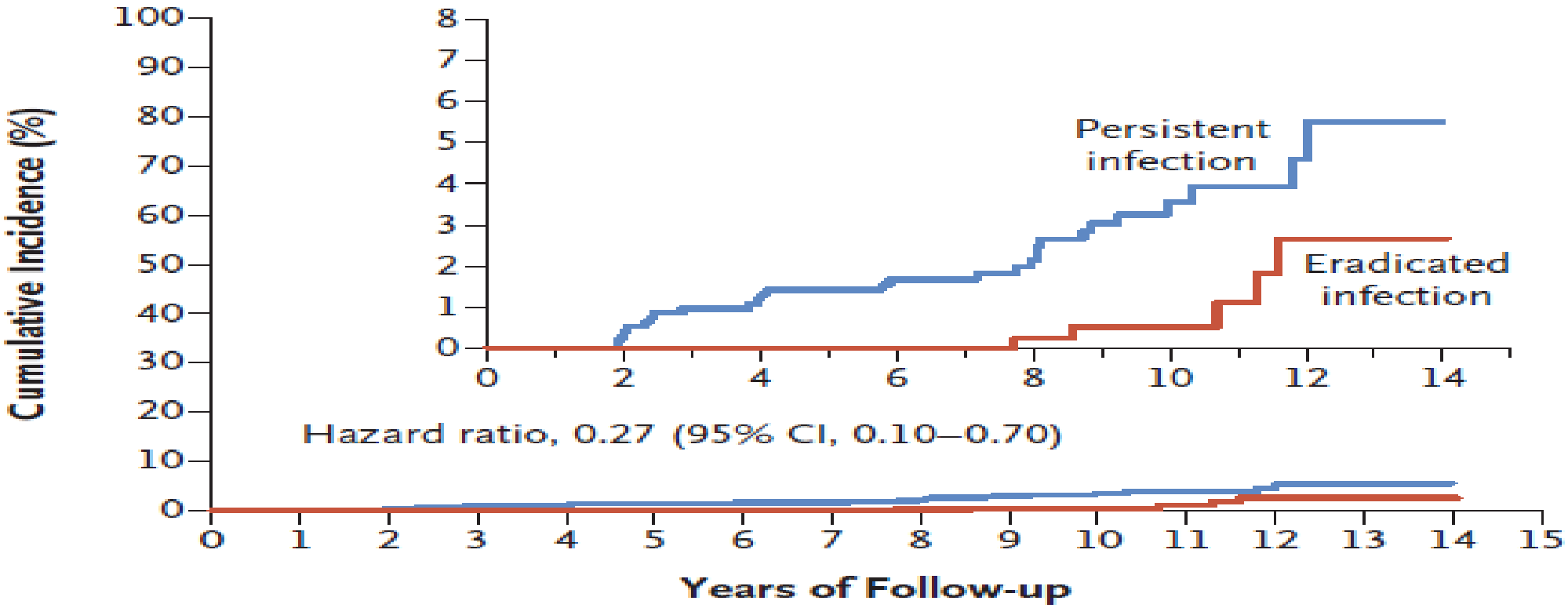
- Metformin, a classical anti-diabetic drug, is known to prevent cancer progression.
- Metformin suppresses gastric cancer progression through calmodulin-like protein 3 secreted from tumor-associated fibroblasts
- Metformin suppresses the expression of Sonic hedgehog in gastric cancer cells
- Metformin inhibits gastric cancer via the inhibition of HIF1α/PKM2 signaling.
- Metformin induces apoptosis and cell cycle arrest in GC cells

Research agenda

Further research is needed, including:

- Large randomized trials in high incidence region with low resource setting e.g. in countries where population based endoscopic surveillance is not available for HP eradication followed by Aspirin /metformin for prevention of GC.

Cumulative Incidence of Gastric Cancer According to H. pylori Eradication Status.



No. at Risk

Persistent infection	979	979	937	899	858	819	743	695	588	482	313	214	105	35	0	0
Eradicated infection	608	608	583	565	547	531	494	465	395	340	221	153	76	27	2	0


Aras
AZERBAIJAN
Baku
Fergana
KYZYLKUM
KYRGYZSTAN
Murat Nehri
ARMENIA
Mount Ararat
Kura
UZBEKISTAN
Amu Darya
Samarkand
TURKEY
KARAKUM DESERT
Chardzhou
TAJIKISTAN
Dushanbe
Lake Van
Diyarbakir
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CASPIAN SEA
Tabriz
TURKMENISTAN
Ashgabat
Lake Urmia
Qezel Owzan
Rasht
Mazar-i-Sharif
Nowshak
SYRIA
Tigris
Mosul
Zanjān
Gorgān
Irbil
Qazvin
Amol
Mashhad
Kirkūk
As Sulaymānīyah
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Tehran
Euphrates
Murgab
Kabul
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KAVIR DESERT
Mount Sikaram
IRAQ
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AFGHANISTAN
Borujerd
Harirud
Ar Ramadi
Baghdad
Khorramābād
Karbala
Al Hillah
Najafabad
Esfahan
Al Amārah
Masjed Soleyman
DASHTELUT
Yazd
Kandahar
Khash
Indus
Helmend
Ahvāz
IRAN
Deri-Ghazi Khan
Quetta
Basra
Kerman
AN NAFUD
Shiraz
KUWAIT
PAKISTAN
Zāhedān
Rahimyar Khan
Sukkur
Larkana
THAR DESERT
Persian Gulf
Ad Dammām
Manama
Nawabshah
Hyderabad
Mirpur Khas
Ash Shaqrā'
Al Hufūf
Doha
Dubai
Karachi
SAUDI ARABIA
Gulf of Oman
Riyadh
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UNITED ARAB EMIRATES
Muscat

Ardabil UMS

NIMAD
NATIONAL INSTITUTE FOR MEDICAL RESEARCH DEVELOPMENT

DDRI Digestive Diseases Research Institute

Effect of Low-Dose Aspirin After H.Pylori eradication on Incidence and Mortality of Gastric Cancer in Northwest of Iran (Ardabil Trial)

Professor Farhad Pourfarzi

This Project (962249) was granted by NIMAD

Research team in Ardabil



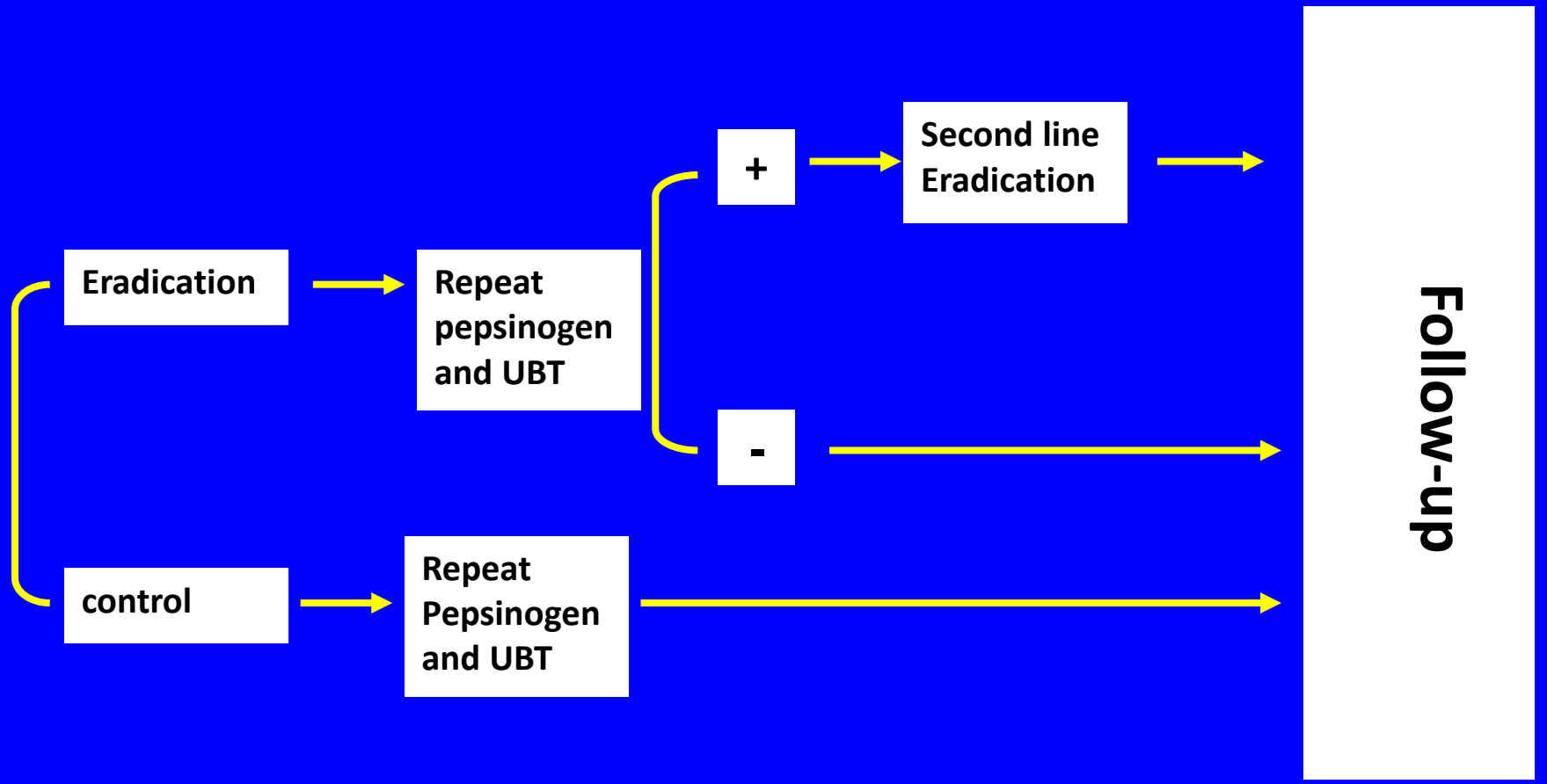
Study Design

- **Study Type:** Parallel-group randomized Controlled Trial
- **Sample size:** 22.000 participants from Ardabil, Iran.
- **Enrolment:** After determining inclusion and exclusion criteria, individuals are enrolled and tested for H pylori (HP) infection using Stool Antigen Test. HP-positive subjects undergo eradication by standard protocol before randomization.
- **Randomization:** Randomization is done using permuted balanced blocks stratified for age and sex.
- **Blindness:** Non of participants and investigator know about assigned medicine (Aspirin and Placebo). .
- **Ethical approval:** It was approved by local ethics committee **(IR.ARUMS.REC.1396.34)**
- **Trial registration:** it was registered **(IRCT20110508203 2N3)**

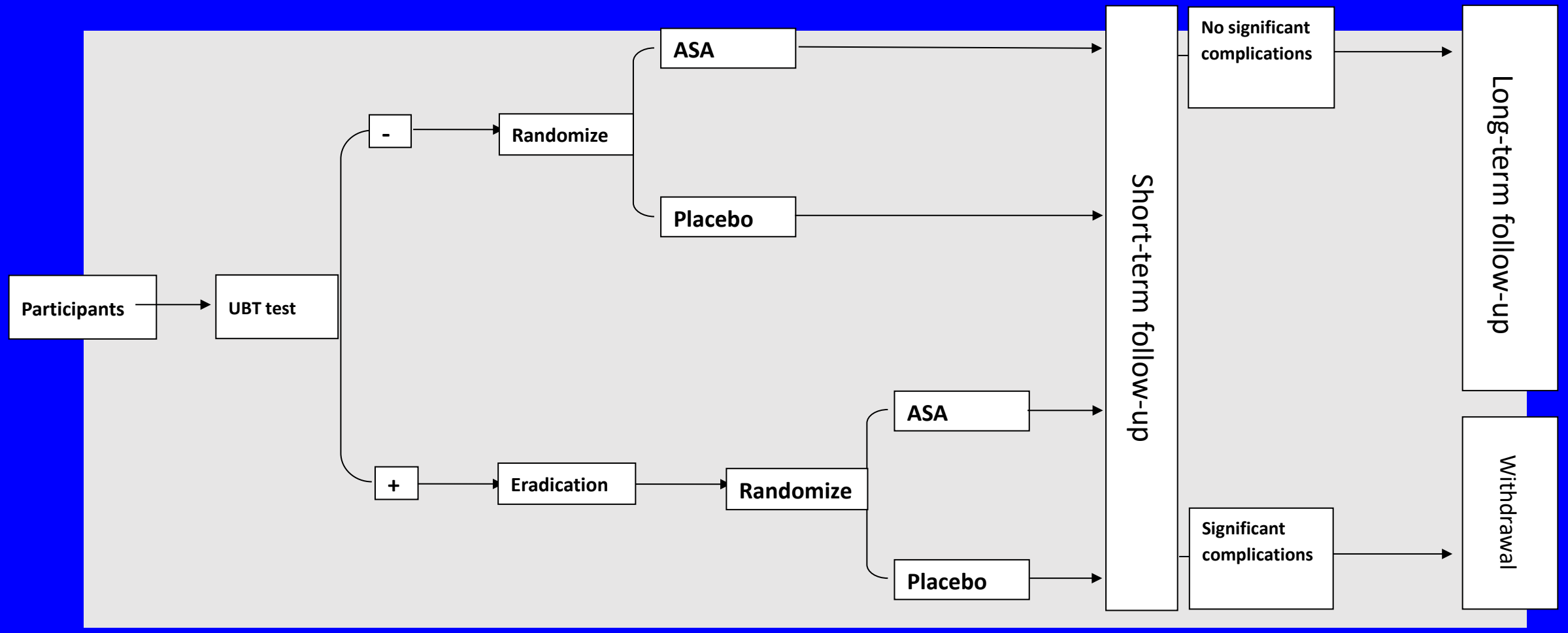
Inclusion Criteria

- Age 35 - 70
- Willing to undergo the treatments and procedures described in the protocol, including up to 4 follow-up visits at 6 weeks, 12 weeks, every 3 months, 5 years and 10 years
- Willing to provide necessary biological specimens
- Willing to sign an informed consent form

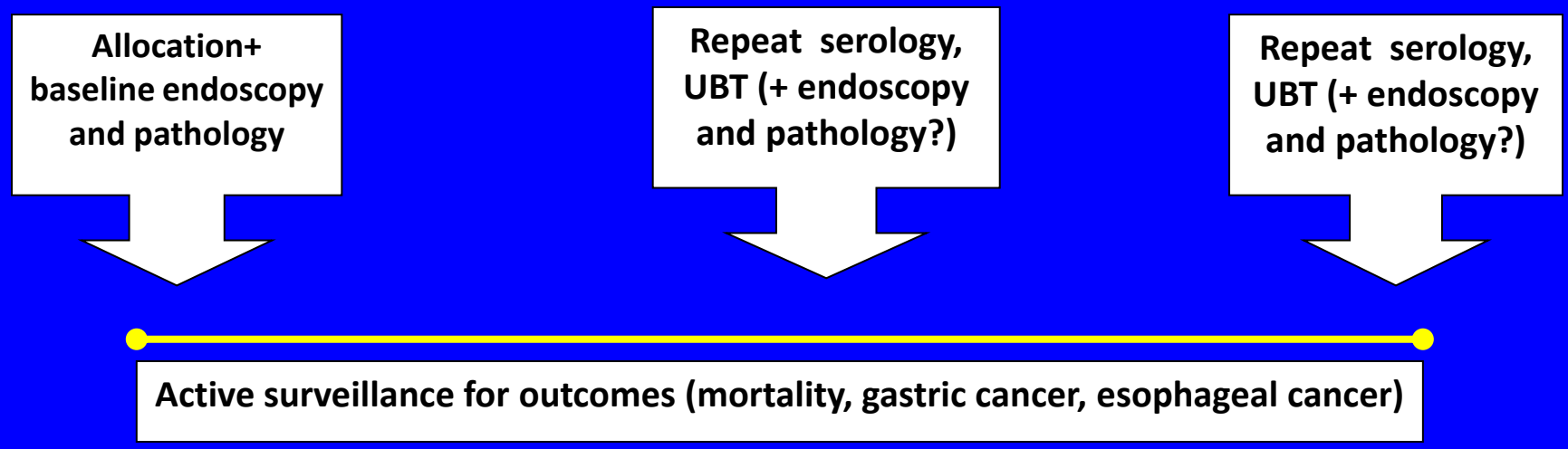
Eradication status



Study Overview



Timeline for 10 years of follow-up (initial plan)

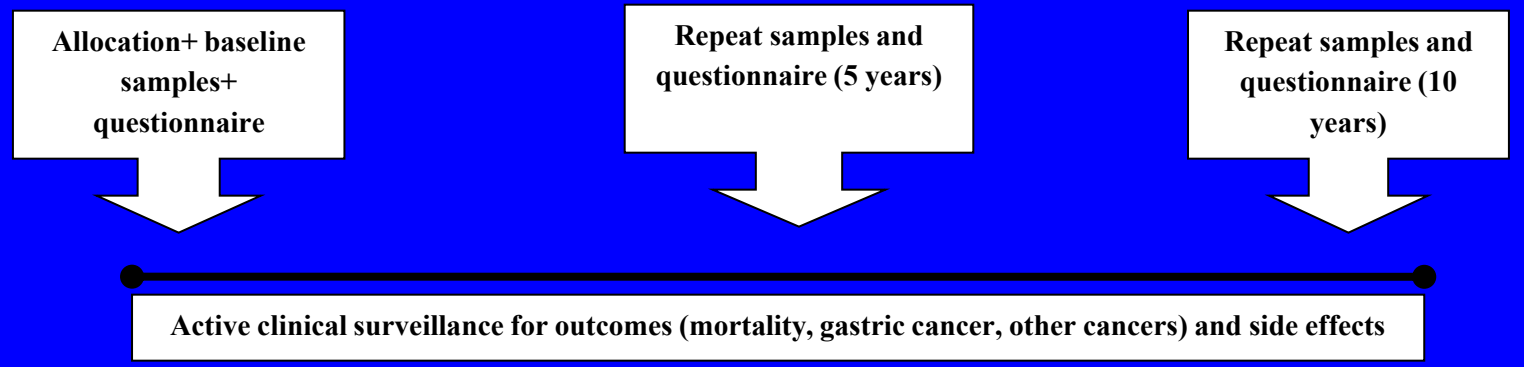


Metformin +Aspirin

- We have recently decided to add a metformin + Aspirin Arm

Follow UP

- **Follow up:** Subjects are followed up for 12 weeks to determine complications. The long term follow up has been started after the 12-week period and will continue **for 10 years**. During these 10 years, participants will be regularly contacted every year to determine outcomes and complications. Also at years 5 and 10 a repeat sampling will be done along with a short follow-up questionnaire.

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BINDER
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BINDER

General Characteristics

Gender	No (%)	Mean Age Years (SD)	Smoker (%)	Alcohol (%)	Drug abuse (%)
Male	8152 (45.9%)	49.8 (±8.6)	3353 (41.2%)	1202 (14.8%)	788 (9.7%)
Female	9615 (54.1 %)	48.5 (±8.7)	161 (1.7%)	38 (0.4%)	23 (0.2%)
Total	17767 (100.0)	49.1 (±8.8)	3514 (19.8%)	1240 (7.0%)	811 (4.5%)

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Subjects BMI

BMI (Kg/ m^2)	Male (%)		Female (%)		Total (%)	
Normal Weight (18.5 – 24.9)	1916	23.5%	939	9.8%	2855	16.1%
Over Weight (25.0 – 29.9)	3970	48.7%	3389	35.2%	7359	41.4%
Class One Obesity	1922	23.6%	3543	36.8%	5465	30.8%
Class Two Obesity	343	4.2%	1744	18.1%	2087	11.7%
Total	8151	100.0%	9615	100.0%	17766	100.0%

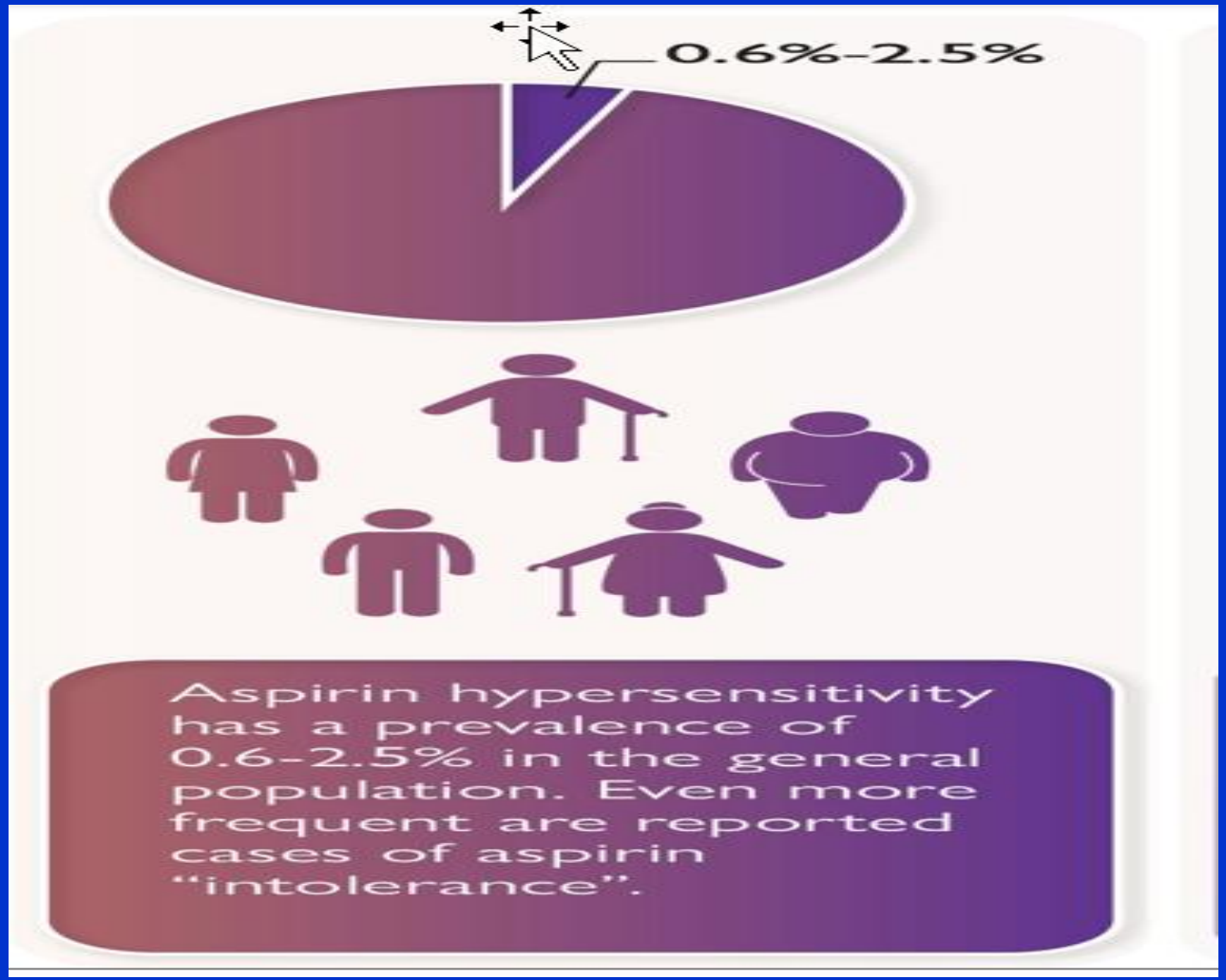
H. Pylori Diagnosis & Treatment

Gender	No (%)	Mean Age Years (SD)	H. Pylori Tested (%)	Positive H. Pylori (%)	H. Pylori Eradication (%)	Successful H. Pylori Eradication (%)
Male	8152 (45.9%)	49.8 (±8.6)	4023	2883 (71.7%)	1820 (63.1%)	1625 (89.3%)
Female	9615 (54.1 %)	48.5 (±8.7)	4602	3159 (68.6%)	3126 (98.9%)	2517 (80.5%)
Total	17767 (100.0%)	49.1 (±8.8)	8625 (100%)	6042 (69.8%)	4946 (81.9%)	4142 (83.8%)

Administered 4-Drug Regimen H. Pylori Eradication

	AGENT	DOSE	ROUTE	DURATION
Regimen A	Omeprazole	20 mg BID	Oral	14 days
	Amoxicillin	1000 mg BID	Oral	14 days
	Furazolidone	200 mg BID	Oral	10 days
	Bismuth subsalicylate	240 mg BID	Oral	14 days
	AGENT	**DOSE**	**ROUTE**	**DURATION**
Regimen B				
	Omeprazole	20 mg BID	Oral	14 days
	Clarithromycin	500 mg BID	Oral	14 days
	Amoxicillin	1000 mg BID	Oral	14 days
	Bismuth subsalicylate	240 mg BID	Oral	14 days

Aspirin-exacerbated respiratory disease to anaphylaxis.



Suggested indication for Aspirin 80 mg per day use in prevention of GI Cancer

- **CRC:** All patients with history of CRC or Polyp .

  First degree family members of patients with CRC and polyp 10 year before the age of cancer.

- **Gastric cancer** :All patients with history of gastric cancer or intestinal metaplasia in gastric mucosa .

  First degree family members of patients with gastric cancer and IM 10 year before the age of cancer.

- Esophageal Adenocarcinoma :All patients with Barret's esophagus

Suggested indication for combination Therapy

- **Statin and Aspirin: for Prevention of HCC in cirrhotic patients**
- **Aspirin and Metformin for prevention of gastric cancer in subject with gastric mucosa intestinal metaplasia**

Thank you

