Association between proximity to industrial chemical installations and cancer mortality in Spain.

Environ Pollut. 2020 Jan 3;260:113869

Abstract
It is likely that pollution from chemical facilities will affect the health of any exposed population; however, the majority of scientific evidence available has focused on occupational exposure rather than environmental. Consequently, this study assessed whether there could have been an excess of cancer-related mortality associated with environmental exposure to pollution from chemical installations — for populations residing in municipalities in the vicinity of chemical industries. To this end, we designed an ecological study which assessed municipal mortality due to 32 types of cancer in the period from 1999 to 2008. The exposure to pollution was estimated using distance from the facilities to the centroid of the municipality as a proxy for exposure. In order to assess any increased cancer mortality risk in municipalities potentially exposed to chemical facilities pollution (situated at a distance of ≤5 km from a chemical installation), we employed Bayesian Hierarchical Poisson Regression Models. This included two Bayesian inference methods: Integrated Nested Laplace Approximations (INLA) and Markov Chain Monte Carlo (MCMC, for validation). The reference category consisted of municipalities beyond the 5 km limit. We found higher mortality risk (relative risk, RR; estimated by INLA, 95% credible interval, 95%CrI) for both sexes for colorectal (RR, 1.09; 95%CrI, 1.05−1.15), gallbladder (1.14; 1.03−1.27), and ovarian cancers (1.10; 1.02−1.20) associated with organic chemical installations. Notably, pleural cancer (2.27; 1.49−3.41) in both sexes was related to fertilizer facilities. Associations were found for women, specifically for ovarian (1.11; 1.01−1.22) and breast cancers (1.06; 1.00−1.13) in the proximity of explosives/pyrotechnics installations; increased breast cancer mortality risk (1.10; 1.03−1.18) was associated with proximity to inorganic chemical installations. The results suggest that environmental exposure to pollutants from some types of chemical facilities may be associated with increased mortality from several different types of cancer.

Using Machine Learning to Construct Nomograms for Patients with Metastatic Colon Cancer.

Colorectal Dis. 2020 Jan 28;:
Authors: Zhao B, Gabriel RA, Vaida F, Eisenstein S, Schnickel GT, Sicklick JK, Clary BM

Abstract
AIM: Patients with synchronous colon cancer metastases have highly variable overall survival (OS), making accurate predictive models challenging to build. We aim to use machine learning to more accurately predict OS in these patients and to present this predictive model in the form of nomograms for patients and clinicians.

METHODS: Using the National Cancer Database (2010–2014), we identified right colon (RC) and left colon (LC) cancer patients with synchronous metastases. Each primary site was split into training and testing datasets. Nomograms predicting 3-year overall survival were created for each site using Cox proportional hazard regression with lasso regression. Each model was evaluated by both calibration (comparison of predicted versus observed overall survival) and validation (degree of concordance as measured by c-index) methodologies.

RESULTS: A total of 11,018 RC and 8,346 LC patients were used to construct and validate the nomograms. After stratifying each model into 5 risk groups, the predicted OS was within the 95% CI of the observed OS in 4 out of 5 risk groups for both the RC and LC models. Externally validated c-indexes at 3 years for RC and LC models were 0.794 and 0.761, respectively.

CONCLUSIONS: Utilization of machine learning can result in more accurate predictive models for patients with metastatic colon cancer. Nomograms built from these models can assist clinicians and patients in the shared decision-making process of their cancer care.

PMID: 31991031 [PubMed — as supplied by publisher]
Theracurmin inhibits intestinal polyp development in Apc-mutant mice by inhibiting inflammation-related factors.

Related Articles

Theracurmin inhibits intestinal polyp development in Apc-mutant mice by inhibiting inflammation-related factors.
Cancer Sci. 2020 Jan 28;:

Abstract
Colorectal cancer (CRC) is the second leading cause of cancer death worldwide. Therefore, it is important to establish useful methods for preventing CRC. One prevention strategy involves the use of cancer chemopreventive agents, including functional foods. We focused on the well-known cancer chemopreventive agent curcumin, which is derived from turmeric. However, curcumin has the disadvantage of being poorly soluble in water due to its high hydrophobicity. To overcome this problem, the formation of submicron particles with surface controlled technology has been applied to curcumin to give it remarkably improved water solubility, and this derived compound is named Theracurmin. To date, the preventive effects of Theracurmin on hereditary intestinal carcinogenesis have not been elucidated. Thus, we used Apc-mutant mice, a model of familial adenomatous polyposis, to evaluate the effects of Theracurmin. First, we showed that treatment with 10~20 µM Theracurmin for 24 hours reduced nuclear factor-kappa B (NF-κB) transcriptional activity in human colon cancer DLD-1 and HCT116 cells. However, treatment with curcumin mixed in water did not change the NF-κB promoter transcriptional activity. As NF-κB is a regulator of inflammation-related factors, we next investigated the downstream targets of NF-κB: monocyte chemoattractant protein-1 (MCP-1) and interleukin (IL)-6. We found that administration of 500 ppm Theracurmin for 8 weeks inhibited intestinal polyp development and suppressed MCP-1 and IL-6 mRNA expression levels in the parts of the intestine with polyps. This report provides a proof of concept for the ongoing Theracurmin human trial (J-CAP-C study).
PMID: 31990962 [PubMed — in process]

Prevalence and association of pks+ Escherichia coli with colorectal cancer in patients at the University Malaya Medical Centre, Malaysia.

Related Articles

Prevalence and association of pks+ Escherichia coli with colorectal cancer in patients at the University Malaya Medical Centre, Malaysia.
Authors: Iyadorai T, Mariappan V, Vellasamy KM, Wanyiri JW, Roslan AC, Lee GK, Sears C, Vadivelu J

Abstract
Escherichia coli (E. coli) from the B2 phylogenetic group is implicated in colorectal cancer (CRC) as it possesses a genomic island, termed polyketide synthetase (pks), which codes for the synthesis of colibactin, a genotoxin that induces DNA damage, cell cycle arrest, mutations and chromosomal instability in eukaryotic cells. The aim of this study was to detect and compare the prevalence of E. coli expressing pks (pks+ E. coli) in CRC patients and healthy controls followed by investigating the virulence triggered by pks+ E. coli using an in-vitro model. Mucosal colon tissues were collected and processed to determine the presence of pks+ E. coli. Thereafter, primary colon epithelial (PCE) and colorectal carcinoma (HCT116) cell lines were used to detect cytopathic response to the isolated pks+ E. coli strains. Our results showed 16.7% and 4.3% of CRC and healthy controls, respectively were pks+ E. coli. Further, PCE displayed syncytia and cell swelling and HCT116 cells, megalocytosis, in response to treatment with the isolated pks+ E. coli strains. In conclusion, pks+ E. coli was more often isolated from tissue of CRC patients compared to healthy individuals, and our in-vitro assays suggest these isolated strains may be involved in the initiation and development of CRC.
PMID: 31990962 [PubMed — in process]

A Single-Center Retrospective Chart Review to Determine Whether the Presence of Comorbidities Affects Colon Cancer Screenings in African Americans.

Related Articles

A Single-Center Retrospective Chart Review to Determine Whether the Presence of Comorbidities Affects Colon Cancer Screenings in African Americans.
Gastroenterol Nurs. 2020 Jan/Feb;43(1):40–52
Authors: Hodges SS
Abstract
Colon cancer is the third leading cause of cancer-related death in African Americans. Although the rates of colon screenings have risen, African Americans remain to be underscreened, and are more likely to present with advanced lesions. This population has a higher prevalence of inflammatory comorbidities, and their effects on screenings have not been fully explored. Along with higher rates of comorbidities, the Southeastern United States is one region for the highest rates of colorectal cancer. The purpose of this study was to determine whether people with comorbidities were more likely to have a screening colonoscopy. Convenience sampling was used to procure 408 patients. The median age was 55 years, and the majority were females (52.2%), who were obese (29.2%), and nonsmokers (52.2%). The most common comorbidity was hypertension (70.3%), followed by osteoarthritis (39%), and diabetes (25.5%). There is a well-documented trend between certain inflammatory comorbidities and higher death rates in patients with colorectal cancer. Clarifying the relationship between comorbidities and cancer starts with screening as many patients as possible. Therefore, interventions that support increasing the number of colorectal cancer screenings are imperative in order to improve morbidity and mortality in this despaired population.
PMID: 31990872 [PubMed — in process]

The cumulative false-positive rate in colorectal cancer screening: a Markov analysis.

Related Articles
The cumulative false-positive rate in colorectal cancer screening: a Markov analysis.
Eur J Gastroenterol Hepatol. 2020 Jan 21;:
Authors: Haug U, Coupé VMH
Abstract
BACKGROUND: Faecal occult blood testing is widely used in colorectal cancer screening. However, there is little empirical long-term evidence on the accumulation of false-positive test results over several screening rounds. We aimed to systematically explore and quantify the cumulative false-positive rate for various scenarios of colorectal cancer screening.
METHODS: Using a Markov analysis, we estimated the lifetime cumulative number of false-positive test results (cumFP) per 100 000 50-year-old persons. We varied the screening interval and the specificity of a single screening test and the starting age of screening.
RESULTS: For a test with a specificity of 98% used from 50 to 74 years, the cumFP at age 74 was 26 260 (1-year interval), 15 102 (2-year interval), and 10 819 (3-year interval), respectively. For a test with a specificity of, respectively, 95 and 92% used at a 2-year interval, the cumFP at age 74 was 2.2 times and 3.0 times higher as compared to a test with a specificity of 98%. The cumFP at age 74 was 18% lower for screening persons aged 54–74 years vs.
50–74 years.
CONCLUSION: Our findings quantitatively illustrate the large variation of the cumFP in colorectal cancer screening between screening strategies, which is relevant to informed decision making and adequate resource planning.
PMID: 31990711 [PubMed — as supplied by publisher]

Lobetyolin induces apoptosis of colon cancer cells by inhibiting glutamine metabolism.

Related Articles
Lobetyolin induces apoptosis of colon cancer cells by inhibiting glutamine metabolism.
J Cell Mol Med. 2020 Jan 28;:
Abstract
The purpose of the present study was to evaluate the anti-cancer property of Lobetyolin on colorectal cancer and explore its potential mechanism. Lobetyolin was incubated with HCT-116 cells in the absence or presence of ASCT2 inhibitor Benser or p53 inhibitor Pifithrin-a. The levels of glutamine, glutamic acid, α-ketoglutarate, ATP and GSH were determined to measure the glutamine metabolism. Annexin V-FITC/PI staining and TUNEL assay were applied to estimate the apoptotic condition. The levels of ASCT2 were examined by RT-qPCR, Western blot and immunofluorescence staining. The expressions of cleaved-caspase-3, caspase-3, cleaved-caspase-7, caspase-7, cleaved-PARP, PARP, p53, p21, bax and survivin were detected using Western blot analysis. As a result, the treatment with Lobetyolin effectively induced apoptosis and glutamine metabolism in HCT-116 cells through ASCT2 signalling. The inhibition of ASCT2 reduced the glutamine-related biomarkers and augmented the apoptotic process. We further found that the effect of Lobetyolin on HCT-116 was related to the expressions of p21 and bax, and transportation of p53 to nucleus. The inhibition of p53 by Pifithrin-a promoted the inhibitory effect of Lobetyolin on ASCT2-mediated apoptosis. Lobetyolin also exerted anti-cancer property in nude mice. In conclusion, the present work suggested that Lobetyolin could induce the apoptosis via the inhibition of ASCT2-mediated glutamine metabolism, which was possibly governed by p53.
PMID: 31990147 [PubMed — as supplied by publisher]
Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data.

Stat Med. 2020 Jan 28;


Abstract
Surrogate endpoints play an important role in drug development when they can be used to measure treatment effect early compared to the final clinical outcome and to predict clinical benefit or harm. Such endpoints are assessed for their predictive value of clinical benefit by investigating the surrogate relationship between treatment effects on the surrogate and final outcomes using meta-analytic methods. When surrogate relationships vary across treatment classes, such validation may fail due to limited data within each treatment class. In this paper, two alternative Bayesian meta-analytic methods are introduced which allow for borrowing of information from other treatment classes when exploring the surrogacy in a particular class. The first approach extends a standard model for the evaluation of surrogate endpoints to a hierarchical meta-analysis model assuming full exchangeability of surrogate relationships across all the treatment classes, thus facilitating borrowing of information across the classes. The second method is able to relax this assumption by allowing for partial exchangeability of surrogate relationships across treatment classes to avoid excessive borrowing of information from distinctly different classes. We carried out a simulation study to assess the proposed methods in nine data scenarios and compared them with subgroup analysis using the standard model within each treatment class. We also applied the methods to an illustrative example in colorectal cancer which led to obtaining the parameters describing the surrogate relationships with higher precision.

PMID: 31990083 [PubMed — as supplied by publisher]

MicroRNA-876-5p represses the cell proliferation and invasion of colorectal cancer through suppressing YAP signaling via targeting RASAL2.

Clin Exp Pharmacol Physiol. 2020 Jan 28;

Authors: Ren L, Zhang Z, Feng Y, Luo M, Hao Z

Abstract
Aberrant expression of microRNA-876-5p (miR-876-5p) is implicated in the progression of multiple human cancers. However, the potential role of miR-876-5p in colorectal cancer remains poorly understood. The purpose of the current study was to investigate the potential role of miR-876-5p in colorectal cancer. miR-876-5p expression was significantly downregulated in colorectal cancer tissues and cell lines compared with normal controls. Gain-of-function assays revealed that miR-876-5p overexpression effectively repressed the malignant behaviors of colorectal cancer cells, including cell proliferation, colony formation, and invasion. Bioinformatics analysis predicted that RAS protein activator like 2 (RASAL2), a potential oncogene for colorectal cancer, is a putative miR-876-5p target gene. A luciferase reporter assay confirmed that miR-876-5p directly binds to the 3′-untranslated region (UTR) of RASAL2. Furthermore, both RASAL2 messenger RNA (mRNA) and protein expression were negatively modulated by miR-876-5p in colorectal cancer cells. Notably, there was an inverse correlation between miR-876-5p and RASAL2 expression in colorectal cancer tissue specimens. Moreover, miR-876-5p was involved in regulating the activation of Yes-associated protein (YAP) signaling through inhibiting RASAL2. However, the miR-876-5p-mediated antitumor effect on colorectal cancer cells was partially reversed by restoring RASAL2 expression. Notably, miR-876-5p upregulation impeded the tumor growth of colorectal cancer cells in vivo in nude mice. Overall, these results demonstrated that miR-876-5p exerts an antitumor function in colorectal cancer by targeting RASAL2 to suppress YAP signaling activation. These findings highlight the importance of the miR-876-5p/RASAL2/YAP axis in colorectal cancer progression and suggest that miR-876-5p is a potential therapeutic target for treating colorectal cancer.

PMID: 31990059 [PubMed — as supplied by publisher]
High stromal nicotinamide N-methyltransferase (NNMT) indicates poor prognosis in colorectal cancer.

Abstract
The presence of lateral lymph node (LLN) metastasis was associated with higher local recurrence risk in patients with lower rectal cancer. The role of LLN dissection has not been fully determined despite prolonged debate that last for few decades. The practical difference between Japan and the West was the main culprit. Japanese used to rely on surgical removal of LLN as local control while the West believed that LLN dissection could be spared after giving neoadjuvant chemoradiotherapy. As time passed, it is getting more common to combine both treatments. With the quality improvement in magnetic resonance imaging, we can now predict the chance of LLN metastasis and evaluate the treatment response with good accuracy. Few large analyses have been published recently and provided us more insight into this topic. In this review, we summarized and provided an update on the latest evidence. We have proposed a treatment algorithm on the management of LLNs which may help clinical decision and provide idea for further research.

PMID: 31989780 [PubMed — as supplied by publisher]

Hyaluronic acid-decorated liposomal nanoparticles for targeted delivery of 5-fluorouracil into HT-29 colorectal cancer cells.

Abstract
The use of liposomes as drug carriers improves the therapeutic efficacy of anticancer drugs, while at the same time reducing side effects. Hyaluronic acid (HA) is recognized by the CD44 receptor, which is overexpressed in many cancer cells. In this study, we developed HA-modified liposomes encapsulating 5-fluorouracil (5-FU) and tested them against a CD44 expressing colorectal cell line (HT29) and a non-CD44 expressing hepatoma cell line. The average size of 5-FU-lipo and 5-FU-lipo-HA nanoparticles were 112 ± 28 and 144 ± 77 nm, respectively. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay showed selective cancer cell death depending on the CD44 expression in a time-dependent manner. Apoptosis assays and cell-cycle analysis indicated that G0/G1 arrest occurred. The colony formation study revealed that cells treated with 5-FU-lipo and 5-FU-lipo-HA had reduced colony formation. Quantitative reverse-transcription polymerase chain reaction study showed that the oncogenic messenger RNA and microRNA levels were significantly reduced in the 5-FU-lipo-HA-treated group, while tumor suppressors were increased in that group. We suggest that optimal targeted delivery and release of 5-FU into colorectal...
cancer cells, renders them susceptible to apoptosis, cell-cycle arrest, and decreased colony formation.

PMID: 31989649 [PubMed — as supplied by publisher]

Modeling rectal cancer to advance neoadjuvant precision therapy.

Abstract
Progress in rectal cancer therapy has been hindered by the lack of effective disease-specific preclinical models that account for the unique molecular profile and biology of rectal cancer. Thus, we developed complementary patient-derived xenograft (PDX) and subsequent in vitro tumor organoid (PDTO) platforms established from pre-neoadjuvant therapy rectal cancer specimens to advance personalized care for rectal cancer patients. Multiple endoscopic samples were obtained from 26 Stage 2 and 3 rectal cancer patients prior to receiving 5FU/RT and implanted subcutaneously into NSG mice to generate 15 subcutaneous PDXs. Second passaged xenografts demonstrated 100% correlation with the corresponding human cancer histology with maintained mutational profiles. Individual rectal cancer PDXs reproduced the 5FU/RT response observed in the corresponding human cancers. Similarly, rectal cancer PDTOs reproduced significant heterogeneity in cellular morphology and architecture. PDTO in vitro 5FU/RT treatment response replicated the clinical 5FU/RT neoadjuvant therapy pathologic response observed in the corresponding patient tumors (p