

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

Red meat consumption and colorectal cancer risk: an integrative review of the international literature.

Red meat consumption and colorectal cancer risk: an integrative review of the international literature

Kathleen Coelho Vieira Moreno

Summary

Colorectal cancer is among the leading causes of cancer death worldwide, and part of this risk is associated with modifiable dietary factors. This integrative review analyzed studies published between 2013 and 2023 in the PubMed, SciELO, ScienceDirect, and LILACS databases on the relationship between red/processed meat consumption and bowel cancer. Consistently, cohort studies and meta-analyses indicate an increased risk of colorectal cancer in individuals with higher intake of these foods, especially processed meats. Proposed mechanisms include the formation of N-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons during high-temperature cooking, as well as the role of heme iron, intestinal dysbiosis, and chronic inflammatory processes in the colonic epithelium. It is concluded that limiting red meat consumption, avoiding processed meats, and adopting dietary patterns rich in fiber and plant-based foods constitute relevant strategies for preventing bowel cancer.

Keywords: red meat; colorectal cancer; intestinal carcinogenesis; processed meat; diet.

Abstract

Colorectal cancer is one of the leading causes of cancer-related deaths worldwide, and part of its risk is linked to modifiable dietary factors. This integrative review examined studies published between 2013 and 2023 in PubMed, SciELO, ScienceDirect and LILACS addressing the relationship between red and processed meat intake and intestinal cancer. Overall, cohort studies and meta-analyses consistently show an increased risk of colorectal cancer among individuals with higher consumption of these foods, particularly processed meats. Proposed mechanisms include the formation of N-nitroso compounds, heterocyclic amines and polycyclic aromatic hydrocarbons during high-temperature cooking, as well as the effects of heme iron, gut dysbiosis and chronic inflammation on the colonic epithelium. It is concluded that limiting red meat intake, avoiding processed meats and adopting dietary patterns rich in fiber and plant-based foods are key strategies for colorectal cancer prevention.

Keywords: red meat; colorectal cancer; intestinal carcinogenesis; processed meat; diet.

1. Introduction

Colorectal cancer is currently one of the major public health challenges. Global estimates indicate approximately 1.9 to 2 million new cases and nearly 1 million deaths per year, which represents approximately 10% of all cancer diagnoses and about 9–10% of cancer deaths are due to cancer. Neoplasms. In high-income countries, such as the United States, Canada, Australia, and much of the world... In Europe, colon and rectal cancers are among the three most common, a worrying trend. of increase in young adults.

Although hereditary factors and genetic syndromes explain a portion of the cases, the majority of the risk is attributed to modifiable determinants, such as dietary patterns, alcohol consumption, smoking, excess weight, and a sedentary lifestyle. Among the components of the diet, meat consumption. Red meat, and especially processed meats, have occupied a central place in the scientific debate since that the International Agency for Research on Cancer (IARC) has classified processed meats as

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

“carcinogenic to humans” (Group 1) and red meat as “probably carcinogenic”

(Group 2A), based on epidemiological and mechanistic evidence.

For nutrition professionals working in clinical, hospital, and sports settings – such as nutritionists who monitor patients in rehabilitation, in gyms or in units of hospitalization – understanding the quality of this evidence is fundamental to guiding decisions. Individualized dietary guidelines and a basis for institutional food policies. In this context, This article seeks to synthesize and critically discuss recent international literature on the relationship between red meat consumption and the risk of bowel cancer, with a focus on colorectal cancer, integrating epidemiological data, proposed biological mechanisms, and health recommendations public.

2. Methodology

This is an integrative literature review. The search was conducted between January 2013 and December 2023 in the PubMed, SciELO, ScienceDirect and LILACS databases, supplemented by Consulting technical documents and reports from leading organizations in cancer and nutrition, such as World Health Organization (WHO), International Agency for Research on Cancer (IARC), World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and American Cancer Society (ACS).

The main descriptors used in English were the terms "red meat" and "colorectal". The terms "cancer," "dietary factors," and "intestinal carcinogenesis," combined using Boolean operators AND. and OR, as well as their Portuguese and Spanish equivalents. Original articles and reviews were included. systematics and meta-analyses available in full, published in Portuguese, English, or Spanish, that to assess the association between the consumption of red meat and/or processed meat and the incidence of Intestinal cancer, especially colorectal cancer.

Experimental studies involving animals, letters to the editor, editorials, and reports were excluded. Case studies and narrative reviews lack a clear description of the search strategy and selection criteria. A The screening of studies occurred in three sequential stages: reading titles, reading abstracts, and reading... in full. For the included articles, standardized information extraction was performed on Study design, population evaluated, method of measuring meat consumption, outcomes in Intestinal cancer and main results. The synthesis of the findings was conducted in a narrative format. seeking to articulate the consistency of quantitative results with the proposed biological plausibility. in literature.

3. Concepts and classification: what is "red meat"?

From an epidemiological point of view, red meat is considered to be muscle meat of

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

Mammals, primarily cattle, pigs, sheep and goats, including fresh, chilled or processed cuts.

Frozen meats. Processed meats, on the other hand, are products that undergo procedures such as... curing, salting, smoking, fermentation or the addition of preservatives with the aim of extending the shelf life durability and modifying sensory characteristics. This category includes processed meats (such as sausages and cured meats), bacon, ham, salami, and some canned meats.

The distinction between fresh red meat and processed meats is crucial in risk analysis. because the strength of the association with colorectal cancer differs between these groups. For processed meats, The evidence in humans is considered sufficient, which led to its classification as... carcinogenic (Group 1). In the case of fresh red meat, the evidence is classified as limited. although supported by plausible biological mechanisms related to heme iron, the formation of N-nitroso compounds and the production of carcinogens during preparation at high temperatures.

In addition to the intrinsic characteristics of the meat and its processing, cultural patterns and Socioeconomic factors influence the amount consumed, the frequency of consumption, and the method of preparation. and the foods that accompany those meals. Thus, the risk is not determined by just one factor. It's not just about an isolated food, but about the context in which it is consumed and the overall dietary pattern, which can... to amplify or attenuate the effects of red meat consumption on intestinal carcinogenesis.

4. Epidemiological overview of colorectal cancer and the role of diet.

Globally, colorectal cancer ranks third in incidence and second in mortality. Mortality is among the most common cancers. In 2020, an estimated 1.9 million new cases and approximately 935,000 deaths were projected, with the highest burden concentrated in countries with a high mortality rate. Human Development, where Western dietary patterns predominate, leads to greater consumption of Meat and ultra-processed foods, and a more sedentary lifestyle.

In the United States, recent data indicates just over 150,000 new diagnoses. Annual cases of colon and rectal cancer and around 50,000 deaths, consolidating the disease as one of the leading causes of cancer death. A decrease in rates is observed in older age groups. This reflects screening programs and improvements in treatment; on the other hand, there is an increase A consistent incidence in adults under 50 years of age, a phenomenon not yet fully understood. explained, but which likely involves interactions between diet, gut microbiota, obesity and Early exposure to ultra-processed foods.

Among the modifiable risk factors, high consumption of red meat stands out and processed food, low intake of fiber and whole grains, excess weight, high consumption of Alcohol, smoking, and physical inactivity are risk factors for colorectal cancer. The literature on diet and colorectal cancer shows, in a way... relatively consistent, with dietary patterns rich in red and processed meats, poor A diet low in fiber, fruits, and vegetables, and associated with high energy density, is linked to a higher risk of...

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

neoplasia. In contrast, Mediterranean or plant-based dietary patterns, with

The predominance of plant-based foods seems to exert a protective effect, in part because promoting a better composition of the gut microbiota, less inflammation, and more effective weight control. bodily.

5. Epidemiological evidence: red meat, processed foods, and the risk of colorectal cancer.

5.1 Classic cohort studies and meta-analyses

The association between meat consumption and colorectal cancer has been documented in Cohort studies dating back to the 1980s and 1990s. Meta-analyses of prospective studies indicate Increased risk of colorectal cancer with high consumption of both red meat and other meats. processed. Chan and colleagues, in a meta-analysis of cohorts, found a relative risk of approximately a 17% higher risk of colorectal cancer for every 100g/day of red meat and an 18% higher risk for every 50g/day of red meat. g/day of processed meats. Subsequent revisions, including the ongoing WCRF/AICR report, They confirmed the existence of a dose-response gradient, in which higher levels of consumption... which translates into greater risk.

A comprehensive synthesis of studies on food, beverages, and the risk of colorectal cancer. The study, led by Vieira and colleagues, reinforced that high intakes of red and processed meat... They are associated with a significantly higher risk of colorectal cancer, while the consumption of milk and grains... Integrals showed an inverse association with the disease. More recent analyses indicate magnitudes similar or slightly lower risk, but maintains the direction of the association: individuals in Those in the highest quintile of red and processed meat consumption tend to present a combined risk. approximately 20–30% higher incidence of colorectal cancer compared to the lowest quintile, even after Adjustments are made for body mass index, smoking, and alcohol consumption.

5.2 Recent evidence and regional heterogeneity

In recent years, various meta-analyses have sought to assess the relationship between meat and meat. Red blood cell count and colorectal cancer persist in distinct cultural contexts. In Asian countries, for example... For example, one review pointed to a significant association between red meat consumption and the risk of... colon and rectal cancer, but did not identify a robust correlation with processed meats, possibly due to lower habitual consumption of these products and differences in processing methods.

More recent syntheses, which separate the types of meat analyzed, suggest that the association is particularly strong for beef and processed pork, while the impact of Lamb and other meats appear to be more modest or difficult to estimate, due to the smaller frequency of consumption in many populations. Still, the body of evidence suggests that High consumption patterns, regardless of the specific origin of the meat, tend to increase. The risk of colorectal cancer is lower when compared to low or moderate intake levels.

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

Dose-response studies indicate that there is no clearly defined "safe threshold".

The IARC summarized that each 50g of processed meat consumed daily is associated with an increase in approximately 18% increased risk of colorectal cancer, and that risk linked to red meat increases with the amount ingested, albeit in a slightly smaller magnitude. In individual terms, this The increase represents a modest absolute risk; however, in populations with high consumption, the impact The cumulative effect on the incidence of colorectal cancer becomes relevant in public health.

5.3 Tumor location, sex, and other modifiers

Some studies suggest differences in the association depending on the intestinal segment. affected. Processed meat tends to show a stronger relationship with rectal cancer and distal portions. of the colon, while fresh red meat shows more moderate associations and, in some cases, not statistically significant in tumors located in the proximal colon.

Differences by sex have also been reported. In several cohorts, the association between meat Processed colorectal cancer is slightly more pronounced in men, which may reflect a higher risk of developing colorectal cancer. consumption, hormonal differences, preparation patterns, or the coexistence of other risk factors, such as higher prevalence of smoking and alcohol consumption in this population.

The interaction with other components of the diet is particularly relevant. Diets rich in Fiber, whole grains, and calcium appear to mitigate some of the risk associated with red meat and processed, possibly due to the dilution effect of carcinogens in the intestinal lumen, modulation favorable microbiota, reduction of intestinal transit time and formation of fatty acids Short-chain anti-inflammatory drugs. For this reason, the main guidelines emphasize this pattern. Nutrition as a whole – and not just the quantity of meat – should be considered when guiding prevention strategies. of colorectal cancer.

6. Biological mechanisms linking red meat and intestinal carcinogenesis

The classification of red meat as a probable carcinogen and of processed meats

The evidence that carcinogens have been identified doesn't rely solely on observational studies. A body of knowledge is needed to understand that this is not the only established basis. Robust body of mechanistic evidence offers biological plausibility for this association, involving Changes in intestinal lumen chemistry, epithelial integrity, and microbiota.

6.1 Heme iron, N-nitroso compounds and oxidative stress

Red meat is rich in heme iron, a highly bioavailable form of the mineral. In animal models and human studies, heme iron promotes the formation of N- compounds. Nitrogens and lipid peroxidation products in the intestinal lumen. These compounds can cause damage. to DNA, induce mutations in colon epithelial cells, and stimulate cell proliferation. Compensatory stages are considered central to the neoplastic transformation process.

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

Human intervention studies show that diets rich in red meat

They elevate fecal markers of N-nitrosation and peroxidation, while dietary patterns with lower meat content or a higher supply of antioxidants reduces these markers. These findings

They support the hypothesis that heme iron and oxidized lipids act synergistically to increase the risk of intestinal carcinogenesis

6.2 Processing, cooking methods and formation of carcinogens

Meat processing through smoking, curing, and the use of nitrites and nitrates promotes formation of nitrosamines and other potentially carcinogenic compounds. In parallel, cooking methods at high temperatures, such as grilling, frying, or roasting over direct heat, lead to formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), substances that, in experimental models, are capable of initiating and promoting tumors in tissue. intestinal.

The combination of meat rich in heme iron, industrial processing with additives

Nitrogenous compounds and intense cooking create an environment conducive to the generation of multiple agents with potential carcinogens, which can act at different stages of carcinogenesis: initiation, promotion and tumor progression. This set of factors helps explain why the risk associated with meat...

The percentage of processed meats generally appears higher and more consistent than that observed for meat. Fresh red.

6.3 Gut microbiota, inflammation and bile acid metabolism

The gut microbiota has emerged as a key element in understanding the link between Diet and colorectal cancer. Diets high in meat and low in fiber are often associated with... reduction of bacteria that produce short-chain fatty acids, such as butyrate, and to the greater abundance of microorganisms capable of metabolizing meat components into pro-inflammatory.

Recent studies suggest that products of bacterial metabolism, such as biogenic amines and derivatives of secondary bile acids can damage the intestinal epithelium and increase stress. local oxidative stress and promote a low-grade chronic inflammatory state, an environment conducive to The emergence of adenomas and adenocarcinomas. Conversely, diets rich in fiber and foods of Plant-based organisms tend to generate a more diverse microbiota profile, with greater production of compounds with anti-inflammatory action and a beneficial effect on the integrity of the colonic mucosa, which This helps explain the protective role of these foods against bowel cancer.

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

7. Limitations, controversies, and uncertainties in the literature

Despite the overall consistency of the association between red meat consumption and cancer

In colorectal cancer, the literature presents methodological challenges and areas of uncertainty that need to be addressed. recognized. Most epidemiological studies are observational and therefore susceptible to Residual confounding and measurement biases. Meat consumption is often assessed by Food frequency questionnaires are instruments subject to recall error and underreporting. Overestimation of portion sizes and frequency.

Another relevant aspect is the strong correlation between meat consumption and other risk factors. such as lower fiber consumption, higher alcohol intake, sedentary lifestyle, and higher body mass index. body. Even with multiple adjustments, it is not always possible to precisely separate the effect. isolating meat from the impact of dietary patterns as a whole can lead to estimates slightly overestimated or underestimated risk attributable to red and processed meat.

Risk estimates also vary between regions. In populations with lower consumption of processed meats or meats with distinct culinary standards, such as those from some Asian countries, the risk The relative association appears more modest and, in certain studies, does not reach significance. Statistics suggest that genetics, microbiota profile, preparation techniques, and cultural context all play a role. They can modify the impact of meat consumption on intestinal carcinogenesis.

Furthermore, relative risk values on the order of 10–20% may seem small when considered individually, which fosters the mistaken perception that the problem would be Irrelevant. In population terms, however, even modest increases translate into thousands. ...of additional cancer cases when high meat consumption is common in a population. For this reason, consensus documents recommend that the interpretation of the findings take into account... Simultaneously, the absolute individual risk and the collective impact on the burden of disease.

Finally, it's important to remember that red meat is also a significant source of protein. High quality, iron, zinc and B vitamins, important nutrients in different stages of life. life cycle. The central issue, therefore, is not to demonize food, but to understand which Quantities, frequencies, and methods of preparation are associated with higher risk, and how to balance this... Consumption should be combined with other food groups in order to preserve nutritional benefits and reduce risk. Exposure to potentially carcinogenic compounds.

8. International recommendations on red meat consumption

Given the convergence of evidence, different health organizations have developed... Guidelines for limiting exposure to red and processed meats. The World Cancer Research The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommends that meat consumption...

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

Cooked red meat should not exceed approximately 350–500 g per week, and meat consumption should be...

Processed materials should be as low as possible. In materials aimed at the public, the American Institute

The study by Cancer Research translates this guideline as something around 12 to 18 ounces of meat per week.

boiled red meat, emphasizing the preference for poultry, fish, and plant-based protein sources in the majority.

part of the meals.

The American Cancer Society, in its guidelines on nutrition and cancer prevention,

It suggests that adults seek dietary patterns predominantly based on foods from

Plant-based diets, limiting red meat and avoiding processed meats whenever possible.

The emphasis is less on an exact number of grams and more on the idea of reducing the frequency of

Consumption of these products, replacing them with legumes, nuts, seeds, fish and poultry.

European and other national organizations adopt similar recommendations, with minor variations.

Variations in specific values depend on the local context. Broadly speaking, there is consensus on three...

Key points: reduce red meat consumption to moderate levels, avoid processed meats during the day.

day and prioritize a dietary pattern rich in fiber, whole grains, fruits, vegetables, and healthy fats.

of the highest quality, such as those found in olive oil, nuts, and fish.

9. Implications for clinical practice and public health

For nutritionists working in private practice, hospitals, gyms, or other services...
rehabilitation, the relationship between red meat and colorectal cancer needs to be translated into

Clear and actionable recommendations. In practice, the most useful message for most patients.

It's not about completely banning red meat, but about building a dietary plan in which it is included.

Food should appear in moderate quantities, accompanied by a high intake of fiber, vegetables, and fruits.
and whole grains, and preferably prepared using gentler cooking methods, such as boiling,
stews and roasts cooked at moderate temperatures.

Among individuals at increased risk – for example, those with a family history
significant colorectal cancer, inflammatory bowel disease, or the presence of advanced polyps –
It may be prudent to adopt even more restrictive limits for red meat and strongly discourage its consumption.
The consumption of processed meats, aligning nutritional guidance with screening strategies,
such as colonoscopy, and regular clinical follow-up.

In the context of public health, policies that promote healthier food environments.
These measures can range from educational campaigns to regulatory measures, such as clearer labeling of...
processed meat products, restricting their availability on school and hospital menus, and encouraging
Culinary preparations based on beans, lentils, chickpeas, and other sources of vegetable protein.
The accumulated experience with dietary guidelines in different countries indicates that changes
Gradual changes in dietary patterns, when supported by policies on pricing, availability, and education,

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023

They have the potential to significantly reduce the burden of chronic diseases, including cancer.

colorectal cancer, in the medium and long term.

By integrating mechanistic knowledge, epidemiological evidence, and recommendations of In international organizations, nutritional practice is beginning to play a strategic role in prevention. of bowel cancer, both in individual care and in the formulation of policies aimed at Promoting health and reducing risk at the population level.

10. Final considerations

The international literature analyzed in this integrative review consistently points to that high consumption of red meat, and especially processed meats, is associated with greater Risk of colorectal cancer. Relative risk estimates generally range from 10–20%. For each typical increase in consumption, with a greater magnitude for processed meats, the effect is more pronounced. evident in populations with Western dietary patterns and plausibility reinforced by mechanisms biological compounds involving heme iron, N-nitroso compounds, and products of high-temperature cooking. Changes in the gut microbiota and low-grade chronic inflammation.

At the same time, it is a modifiable risk factor, the impact of which can be Substantially reduced by adjustments in dietary patterns. Guidelines from international organizations. They converge on the recommendation to limit red meat consumption to moderate levels, and to avoid... Routine use of processed meats and prioritize a diet rich in plant-based foods and whole grains. whole foods and less aggressive preparation methods, inserted in a context of promoting Physical activity and body weight control.

For healthcare professionals who work with people at different stages of life – from From patients in the ICU to athletes seeking peak performance, including individuals recovering from Whether it's chemical dependency or weight loss, the central message is one of balance. informed. The goal is not to turn red meat into an absolute villain, but to help each patient. to understand that repeated food choices over decades, especially when High volumes of processed meats and low fiber intake are reflected in risks that... They can be prevented.

In this context, evidence-based nutrition plays a crucial role: translating results. Transforming complex studies into understandable recommendations, respecting food culture, and at the same time... In time, we need to offer concrete alternatives so that the pleasure of eating can coexist with a real reduction in costs. of the risk of bowel cancer. By linking clinical practice, nutritional education and public policies of In promoting health, the professional expands the possibility of impacting not only the outcome. This will affect not only the individual burden of colorectal cancer, but also the population-based burden in the coming decades.

Year III, v.2 2023 | Submission: 04/12/2023 | Accepted: 06/12/2023 | Publication: 08/12/2023
References

BOUVARD, V. et al. *Carcinogenicity of consumption of red and processed meat*. Lancet Oncology, London, vol. 16, no. 16, p. 1599-1600, 2015.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. *Red meat and processed meat*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, v. 114. Lyon: IARC, 2018.

WORLD CANCER RESEARCH FUND; AMERICAN INSTITUTE FOR CANCER RESEARCH. *Diet, nutrition, physical activity and colorectal cancer. Continuous Update Project Expert Report*. London: WCRF/AICR, 2018.

CHAN, DSM et al. *Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies*. PLoS ONE, San Francisco, v. 6, no. 6, e20456, 2011.

VIEIRA, AR et al. *Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project*. Annals of Oncology, Oxford, vol. 28, no. 8, p. 1788-1802, 2017.

BENARBA, B. *Red and processed meat and colorectal cancer: an update*. EXCLI Journal, Hannover, v. 17, p. 792-797, 2018.

DI, Y. et al. *Association of meat consumption with the risk of gastrointestinal cancers: a systematic review and meta-analysis*. BMC Cancer, London, vol. 23, art. 11218, 2023.

KRUGER, C.; ZHOU, Y. *Red meat and colon cancer: a review of mechanistic evidence for heme in the context of risk assessment methodology*. Food and Chemical Toxicology, Oxford, vol. 118, p. 861-870, 2018.

CROSS, AJ; POLLOCK, JRA; BINGHAM, SA *Haem iron and endogenous intestinal N-nitrosation arising from red meat*. Cancer Research, Philadelphia, vol. 63, no. 10, p. 2358-2360, 2003.

DIAKITÉ, MT et al. *Relationships between gut microbiota, red meat consumption and colorectal cancer*. Microorganisms, Basel, v. 10, no. 5, 951, 2022.

LOKE, YL et al. *Colon carcinogenesis: the interplay between diet and gut microbiota*. Frontiers in Cellular and Infection Microbiology, Lausanne, v. 10, 2020.

WORLD HEALTH ORGANIZATION. *Colorectal cancer: fact sheet*. Geneva: WHO, 2023.

AMERICAN CANCER SOCIETY. *Colorectal Cancer Facts & Figures 2023*. Atlanta: American Cancer Society, 2023.

ROCK, CL et al. *American Cancer Society guideline for diet and physical activity for cancer prevention*. CA: A Cancer Journal for Clinicians, Atlanta, vol. 70, no. 4, p. 245-271, 2020.

AMERICAN INSTITUTE FOR CANCER RESEARCH. *Limit consumption of red and processed meat*. Arlington: AICR, 2023.

SUNG, H. et al. *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA: A Cancer Journal for Clinicians, Atlanta, vol. 71, no. 3, p. 209-249, 2021.