

in the name of God

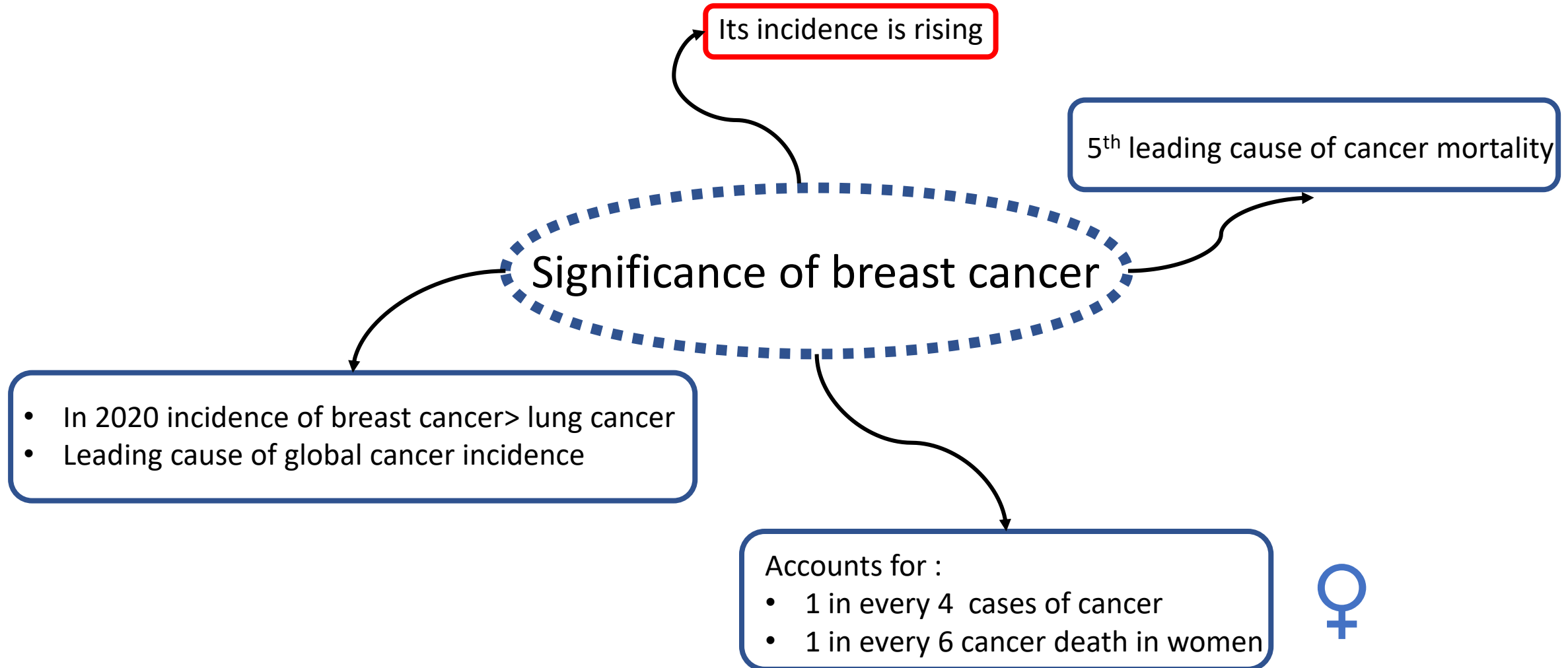
Association between Consumption of Artificial Sweeteners and Breast Cancer Risk: A Systematic Review and Meta-Analysis of Observational Studies

Nutrition and Cancer, 75:3

Journal club- 8/4/2023

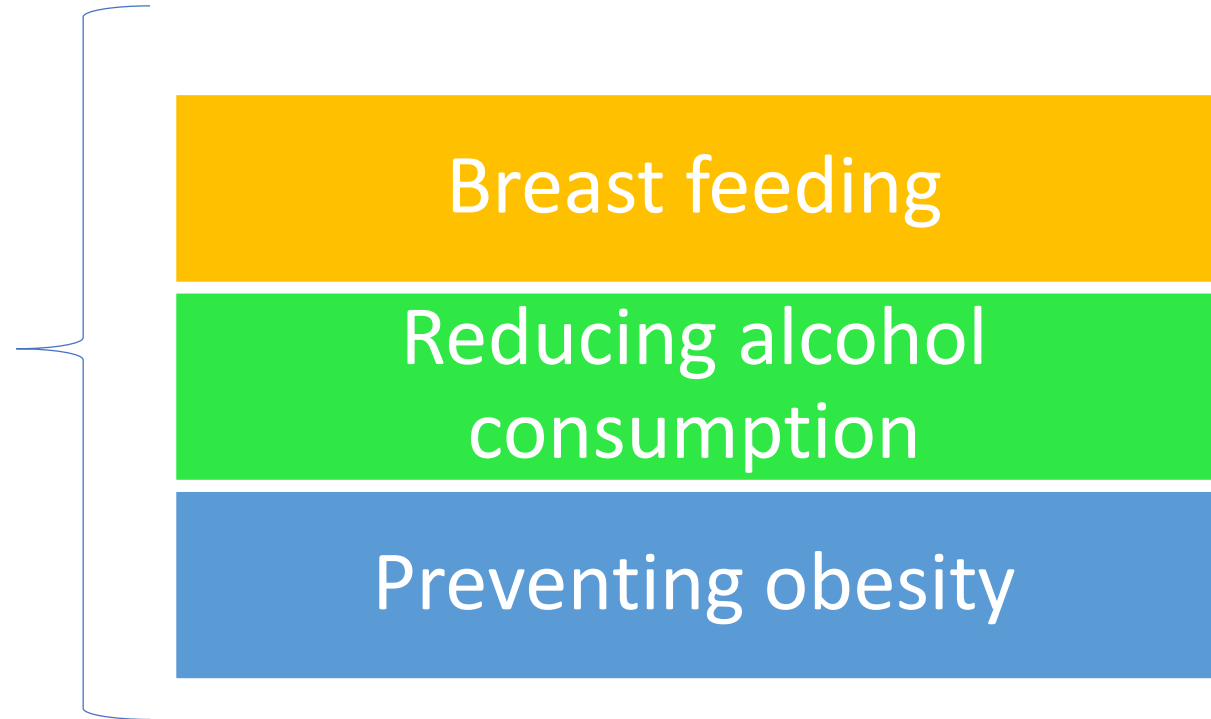
Presentation by: Maede mousavi

introduction



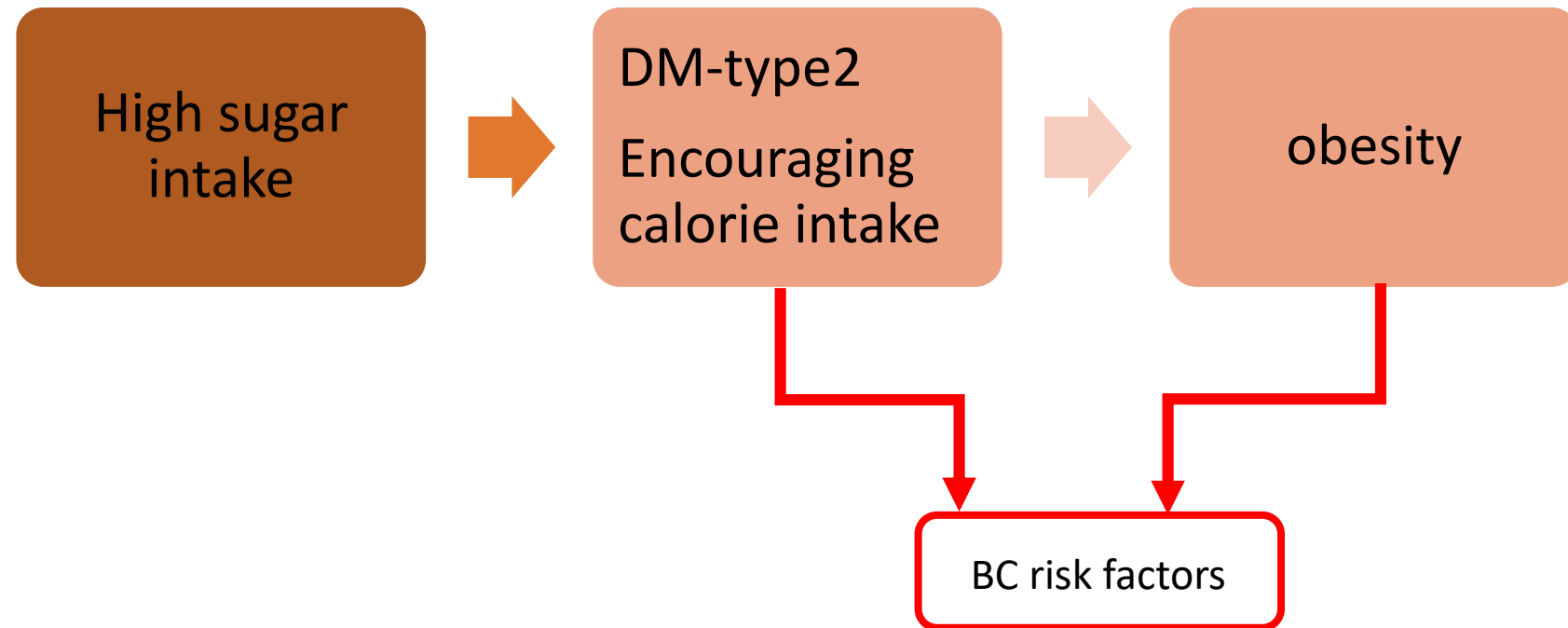
introduction

Factors that likely reduce the risk of breast cancer incidence



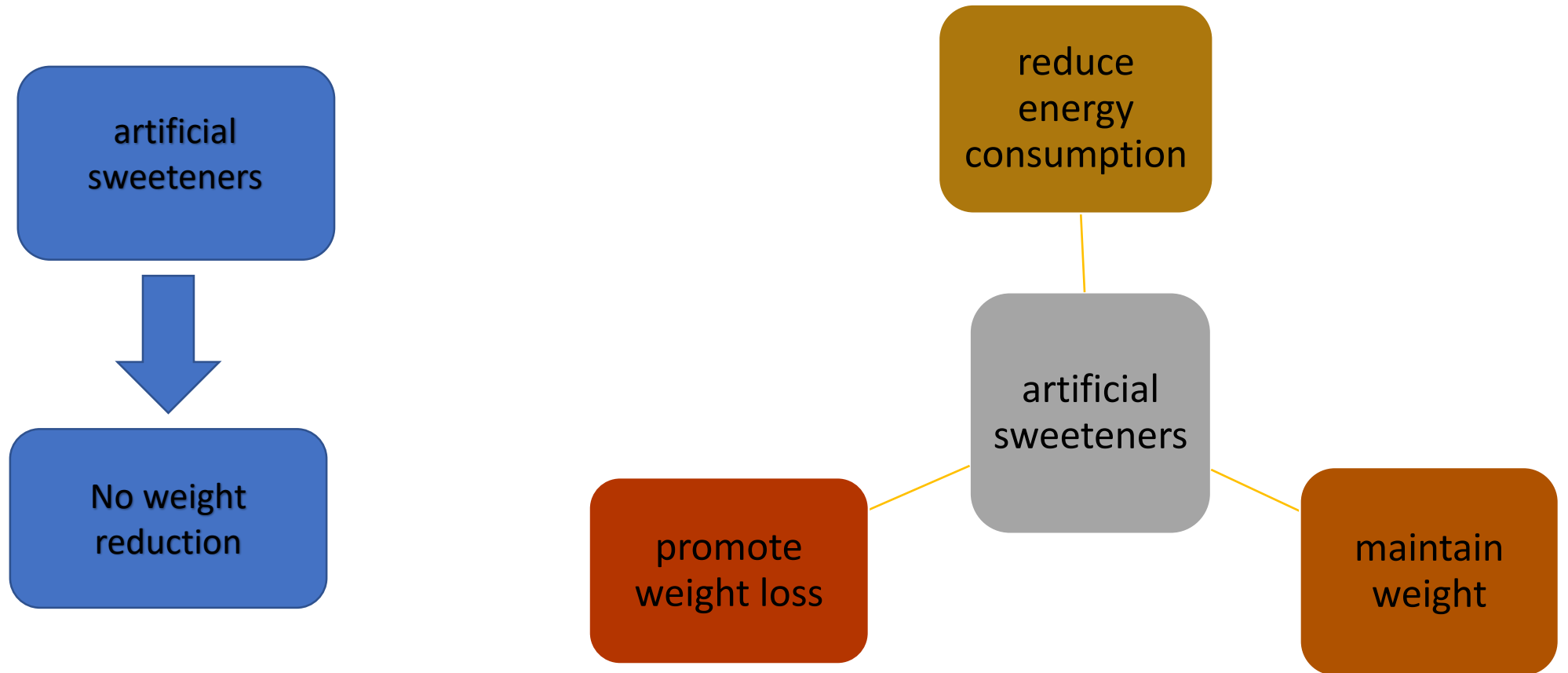
introduction

- Artificial sweetener :a substance that can be added to foods and beverages in place of sugar
- Examples: saccharin, aspartame, cyclamate, and acesulfame potassium



introduction

Opposing results of different studies



introduction

An Italian study from
2007: the incidence of BC
is negatively correlated
with the intake of
artificial sweeteners

a French study in 2022
consumers of total
artificial sweeteners,
were associated with an
increased risk of BC

introduction

Up to now:

no systematic review on the relationship
between artificial sweeteners and the risk of BC



Aim of this study: analyzing and synthesizing the
data on these substances and BC.

methods

Inclusion criteria

participants without BC (cohort study) at the time of recruitment or previous history of BC (case-control study).

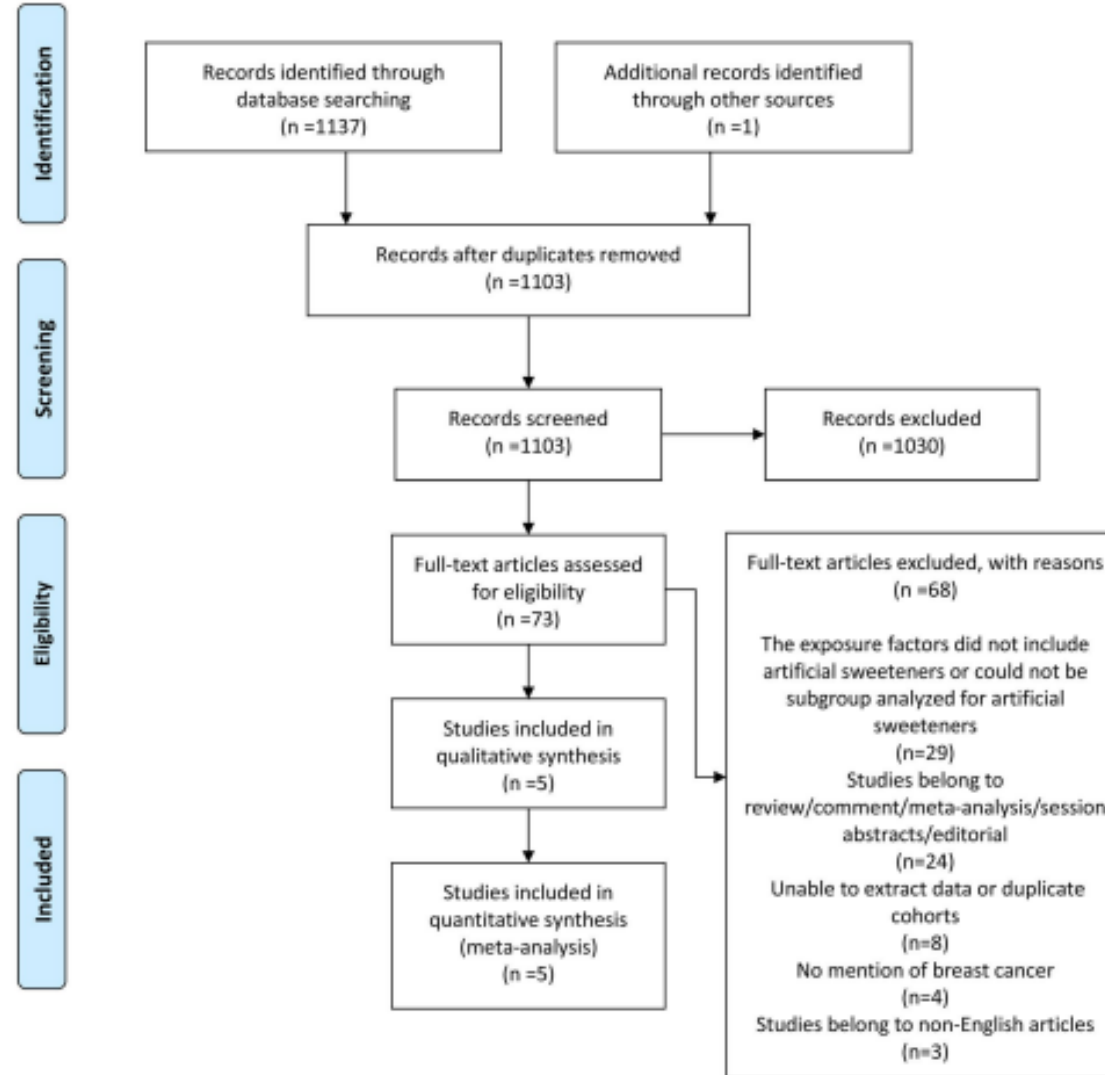
The exposed group was exposed to any type or dose of artificial sweeteners, and the non-exposed group was not exposed to artificial sweeteners.

The incidence of BC was taken as the result.

The study is a case-control, prospective or retrospective cohort study.



PRISMA 2009 Flow Diagram



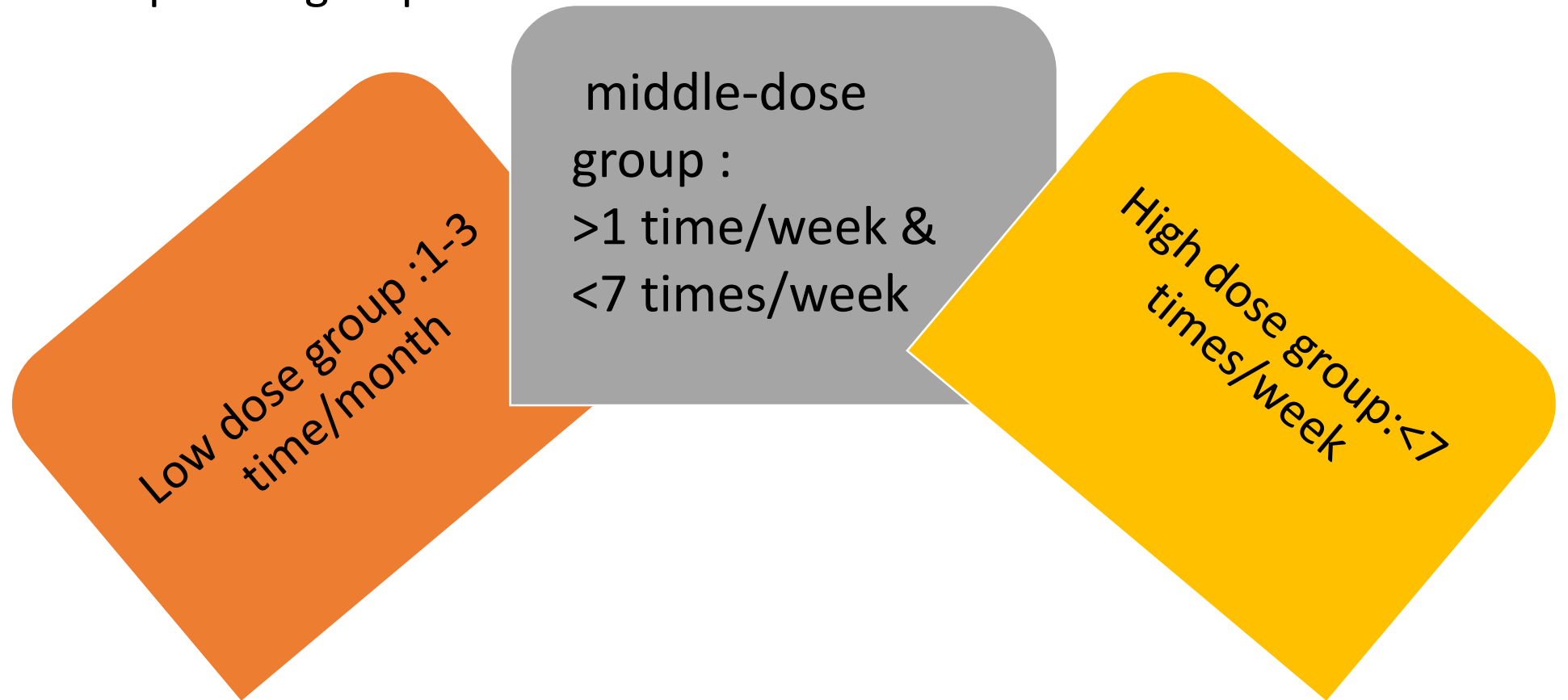
A schematic flow for the selection of articles included in this meta-analysis

methods

- one study each was conducted in these countries, Denmark, Italy, Australia, America, and France.
- The time of the experiment :1984 to 2021, and the articles were published between 1990 and 2022.
- The exposure assessment: questionnaire or interview.
- The cohort studies were conducted in MCCS, NHS, NHSII and NutriNet-Santé
- enrolled 314,056 participants in total, of which 13,304 suffered from the BC.
- In case-control studies, they included 4,043 cancer cases and 3,910 controls.
- the recruitment age: 18 to 70 and the median follow-up time: 7.8 to 11.6
- Age adjustment: in every analysis,
- the remaining: place of residence, SEIFA, smoking, alcohol drinking, physical activity, BMI, total energy intake, consumption of hot beverages, family history of BC, etc
- The quality of all the studies were assessed using the Newcastle-Ottawa Scale

methods

Classification of exposure group:



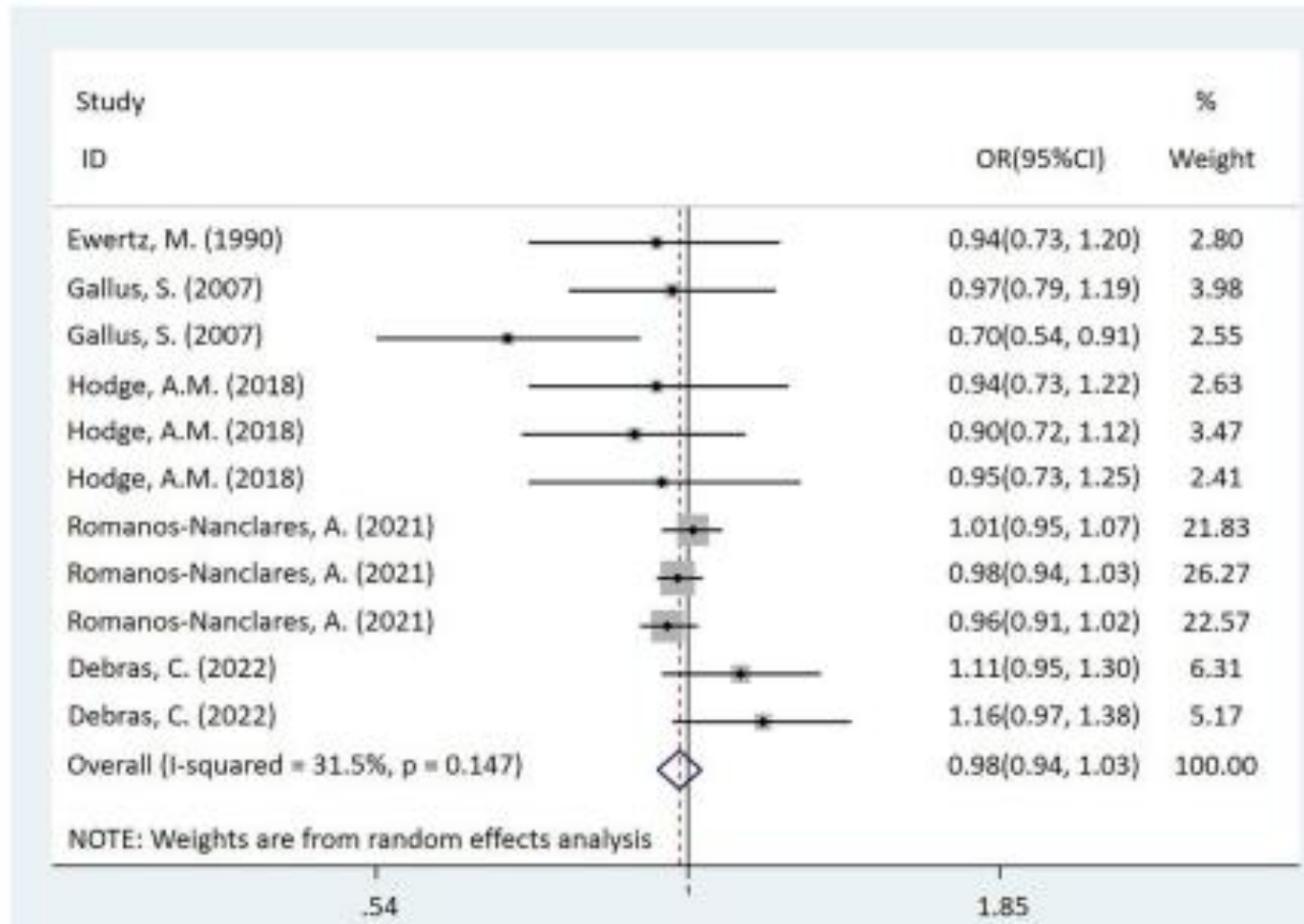
The intake of non-exposure group or very-low-dose group was < once a month

results

- 5 studies were included in the systematic review, 2 case-control studies and three cohort studies.
- Artificial Sweeteners and Risk of Breast Cancer: In this meta-analysis, the participant exposed to artificial sweeteners had no different incidence of BC from the non-exposure group (OR = 0.98, 95%CI = [0.94-1.03], $p = 0.450$)

results

Forest diagram of artificial sweeteners exposure and breast cancer incidence (p=0.450)



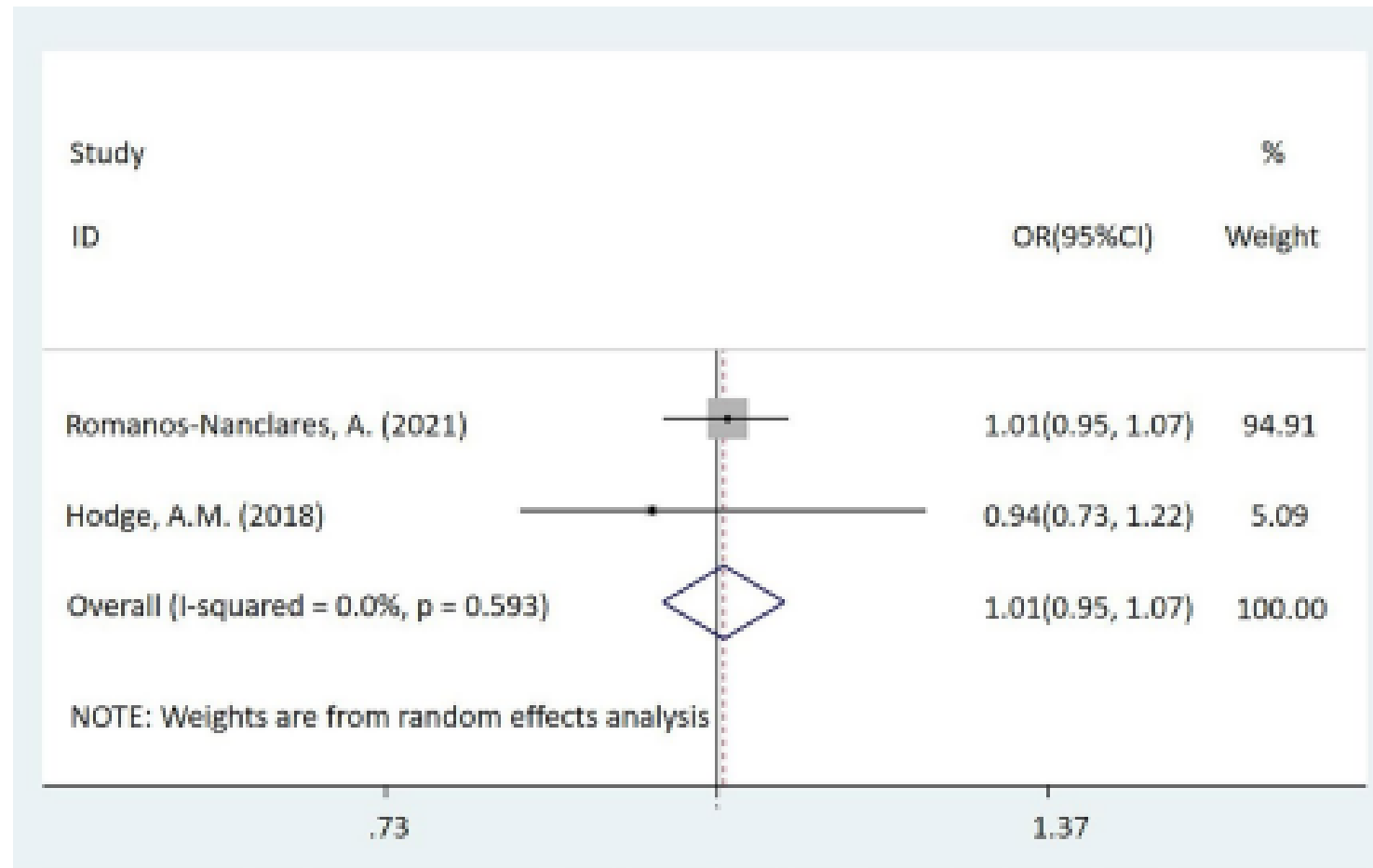
Results

separation of the study based on dosage

- The low and middle dose groups were included in two cohort studies
- the high-dose group was included in three studies, which were two cohort studies and one case-control study respectively
- Subgroup analysis: compared with the non-exposure/very-low-dose group, the incidence of BC had no difference in the population exposed to low-dose artificial sweeteners

(OR = 1.01, 95%CI = [0.95-1.07], p = 0.831)

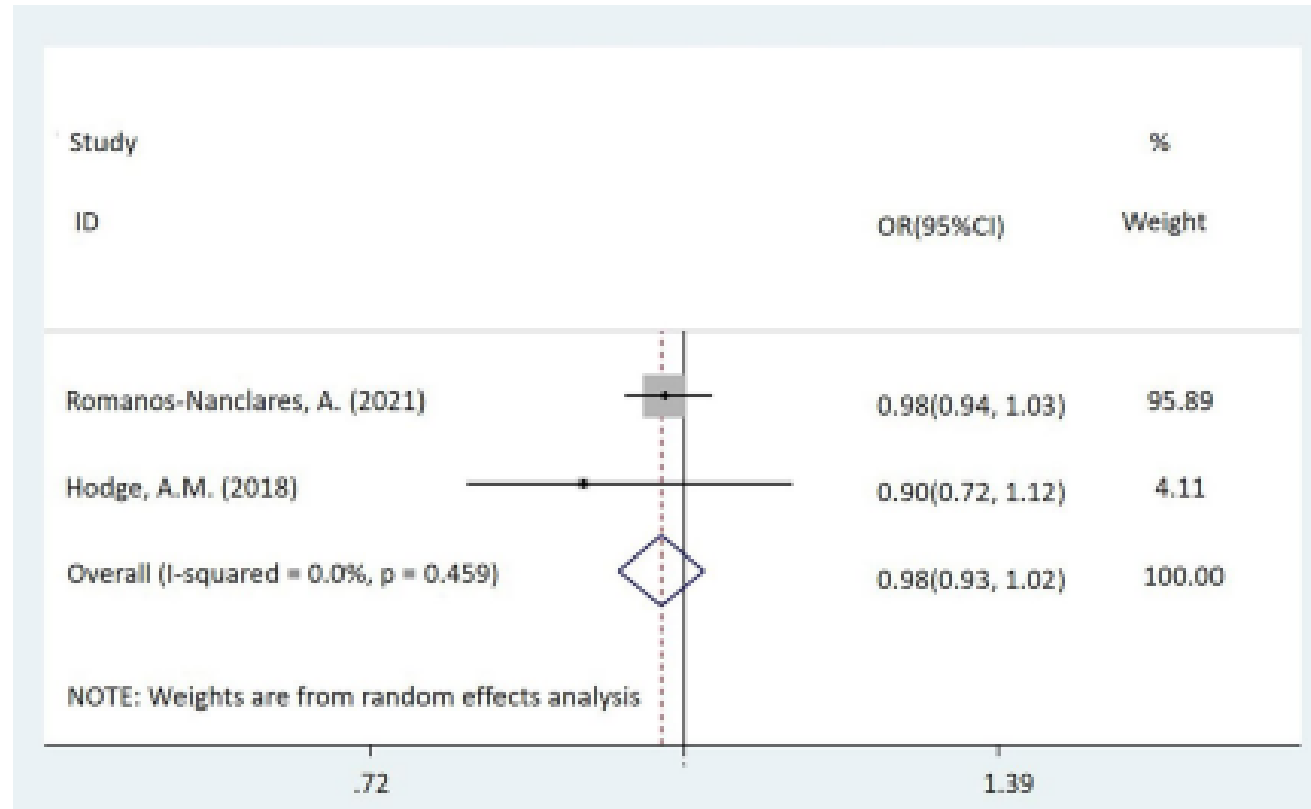
results



Forest plot of low-dose artificial sweeteners exposure and incidence of breast cancer ($p = 0.831$).

results

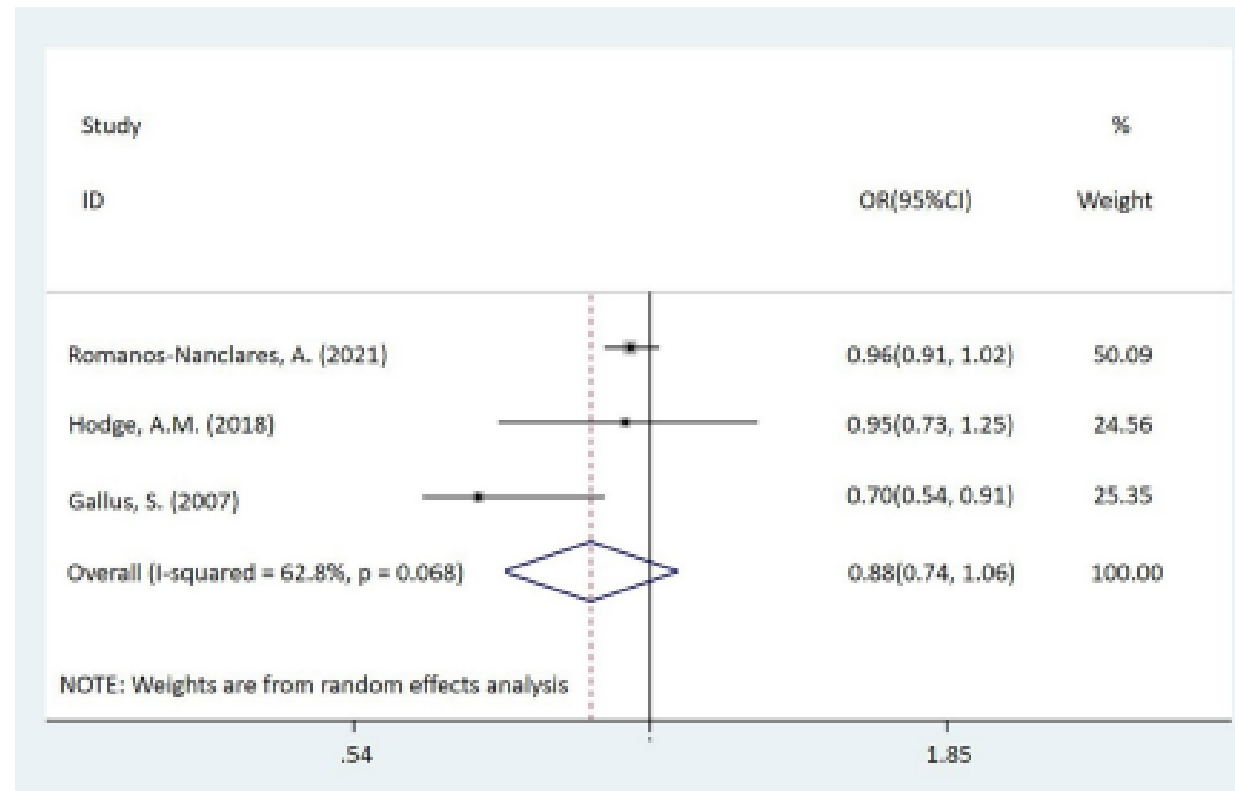
In the middle-dose group: no difference in the incidence of BC between the exposed and the non-exposed/very-low-dose group (OR = 0.98, 95%CI = [0.93-1.02], p = 0.299)



Forest plot of middle-dose artificial sweeteners exposure and incidence of breast cancer (p=0.299).

results

Compared with the non-exposure/very-low-dose group, the incidence of BC also had no difference in the population exposed to high-dose artificial sweeteners (OR = 0.88, 95%CI = [0.74-1.06], $p = 0.185$)




Forest plot of high-dose artificial sweeteners exposure and incidence of breast cancer ($p=0.185$).


discussion

- there was no statistical significance link between artificial sweeteners and BC. Furthermore,
- the results of subgroup analysis: no relationship between the exposure dose and the prevalence of BC.

discussion

- Artificial sweeteners are calorie-free
- reduce sugar consumption  lower insulin and satiety
- Help reducing weight
- Lower the risk of DM-2 when compared to sucrose
- desserts, sweets, and diets high in refined sugar may increase the risk of BC in women
- The relevant mechanisms of sweetness and obesity: insulin resistance, hyperinsulinemia, increased bioavailability of steroid hormones, oxidative stress, and inflammation

discussion

- these metabolic alterations produce a setting that favors the development and spread of malignancies.
- High sugar consumption  independently induce chronic activation of the insulin signaling system and elevation of indicators of oxidative stress and inflammation, which together raise the risk of BC
- obesity does not significantly increase the incidence of BC in premenopausal women
- postmenopausal overweight women have higher chance of developing the disease than slim women


discussion

- the risk of BC in patients with type 2 diabetes increased by 23%
- there is a positive correlation between type 2 diabetes and the incidence rate of BC during the 10-year follow-up

Discussion






molecular point of view

Different subtypes of BC based on hormone expression	Estrogen receptor
	Progesterone receptor
	Human epidermal growth factor-2 receptor (HER-2)

- HER-2 and hyperglycemia and insulin resistance (IR) have been shown to be linked
- DM-2 patients  higher circulating HER-2 concentrations
- the normal levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2) in overweight people as well as the rise in insulin levels may cause an over-activation of the IR and IGF-1R pathways. Because the signal transduction mediated by IR/ IGF-1R will further boost HER-2 synthesis, encourage cancer cell proliferation and spread, and hinder cancer

Discussion

molecular point of view

- Adipose tissue  primary source of estrogen synthesis after menopause  obesity raise the risk of BC in postmenopausal women
- Obesity caused by high glucose  more adipose tissue  estrogen-sensitive breast tissue will receive more estrogen stimulation, while estradiol (E2) stimulates cell growth through the role of estrogen receptor  replication errors during mitosis and mutations

Derived from the
these mechanisms,
artificial sweeteners
seem to reduce the
incidence of BC

This research results
show that there is no
relationship between
artificial sweeteners
and BC.

no artificial sweetener has been consistently linked to negative health consequences, and according to FDA inspection

Discussion

- the carcinogenic risk of artificial sweeteners is still debatable
- certain of its by-products, such as formaldehyde, a by-product of aspartame metabolism, are known carcinogens.
- Formaldehyde is a high-risk factor for triggering BC
- it can break down the BRCA2 protein, a tumor suppressor protein.
- Artificial sweeteners and the risk of BC have conflicting findings. Most studies showed no association, but some studies showed that the risk was reduced

- Aspartame and potassium acetylsulfate were the two specific artificial sweeteners that were linked to an increased risk of BC
- But with no statistically significant relationship between the total amount of artificial sweeteners and BC risk

conclusion

- there is no relationship between the exposure of artificial sweeteners and the incidence of BC.
- due to the limitation of this study, more large-scale studies are needed to further explore