**Exploring the Nexus: BPA and Human Cancer - A Systematic Literature Review**

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**ABSTRACT**

Bisphenol A (BPA), a synthetic compound with estrogenic properties, has become a subject of increasing concern due to its wide presence in consumer products and its potential endocrine-disrupting effects. BPA exposure has also been associated with the risk of developing various types of cancer, such as breast, prostate, thyroid, and colorectal cancers. This paper reviewed the literature on the association between BPA exposure and cancer in humans, and identified the gaps and challenges in the current research. A systematic review of the literature was conducted to evaluate the association between BPA exposure and cancer in humans, and to identify the gaps and challenges in the current research. The review followed the PICO framework, where the human population (P) was the central focus, and the exposure (I) to BPA was examined, with a comparison drawn to individuals with no or very low BPA exposure (C). The primary outcome of interest was the prevalence, incidence, or risk of developing various types of cancer (O) in participants across the selected studies. The review included 31 studies that met the predefined inclusion and exclusion criteria, covering a range of cancer types and geographic regions. The paper evaluated the quality and reliability of the studies, and discussed the main findings, limitations, and implications of the literature. Based on the findings this review concluded that the current evidence is mixed and inconclusive, and suggested that future studies should address the methodological and analytical challenges in measuring BPA exposure and its effects on cancer.

**INTRODUCTION**

Over recent decades, environmental factors have increasingly come under scrutiny for their potential role in human health, particularly concerning the development and progression of various diseases. Among these factors, Bisphenol A (BPA), a synthetic compound widely used in the production of polyplastics, has emerged as a subject of growing concern. Bisphenol A (BPA), alternatively referred to as 2,2-bis(4-hydroxyphenyl)propane, is an synthetic organic compound classified as both a derivative of diphenylmethane and a member of the bisphenols group.1

Manufacturers produce more than 8 billion pounds of BPA each year, making it one of the extensively utilized compounds in the industry.2 BPA is widely used in the production of polycarbonate (PC) plastics and epoxy resins due to it’s chemical constitution and ability to form chemical bonds between molecules. While air, dust, and water are other possible sources of exposure, BPA in food and beverages account for the majority of daily human exposure. In addition to various food and drink containers, polycarbonate (PC) is used in water and infant baby bottles, microwave-safe items, compact discs, impact-resistant safety equipment, and medical devices, particularly those used in hospitals, polycarbonate polymers have a wide range of uses. Epoxy resins are utilized as coatings on metal lids for glass jars and bottles, including those used to store newborn formula, as well as protective linings for a range of canned goods and drinks.3-5 The release of BPA from bottles into water and various beverages leads to human exposure. BPA can potentially leach into food from both polycarbonate plastic items and containers lined with epoxy resin. Interestingly, it seems that temperature plays a more significant role in this leaching process than the age of the container; heating plastic, as in the case of microwave usage, intensifies the release of BPA into liquids.6

People are concerned about BPA for a number of reasons, including it’s wide spread exposure to humans and the health risks caused by it. According to the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) in 2003–2004, detectable levels of BPA are present in urinary samples of more than 90% of Americans aged six and older.7,8 Since the body metabolizes BPA rapidly, the high frequency of detection indicates that exposures are occurring frequently among people.9 BPA has been detected in a number of tissues, including human fetal livers, breast milk, follicular and amniotic fluid, pregnant women's serum, and the placental and cord blood of fetuses. This indicates the possibility of BPA exposure at multiple stages of life, including prenatal development.10-17 Likewise, the detection of urine BPA levels in people from diverse populations, both urban and rural, suggests that BPA exposure is not restricted to any particular geographic region or community.18 This extensive detection of BPA in urine, serum, and various bodily fluids and tissues across diverse demographic groups underscores the exposure of humans to this compound and indicates that it is a common environmental contaminant.

Notwithstanding the extensive exposure, BPA concentrations in humans are often thought to be lower than those linked to effects in standardized toxicological studies performed in accordance with recognized protocols.19 The US Environmental Protection Agency (EPA) has defined limits for BPA exposure. The lowest-observed-effect limit (LOAEL) is 50 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is 5 mg/kg body weight/day. For children under two years old, the estimated daily intake (EDI) of BPA is 1.1 (μg/kg/day), while for those over two, it is 0.5 (μg/kg/day).20 A tentative temporary tolerable daily intake (t-TDI) of 4 μg/kg body weight per day has been established for Bisphenol A (BPA) by the European Food Safety Authority (EFSA), taking into account the substance's endocrine disrupting properties.21 Median estimated BPA intakes (ng/kg-dy) for Canada from 2009 till 2015 remained relatively stable 19.2–22.4 ng/kg-day and decreased for the United States from 32.1 to 21.6 ng/kg-day for ∼2009–2014 time period. In contrast, over the same duration intakes in Korea appeared to increase from 15.5 to 24.2 ng/kg-day. 1.34 μg/L for children aged 6 to 11 and 1.24 μg/L for adults were the estimated median concentrations of total BPA in urine.22

Despite current regulatory guidelines suggesting that exposure to Bisphenol A (BPA) is generally within safe limits,23 scientists and researchers maintain concerns for several compelling reasons. Data from in vitro and in vivo studies on humans and animals indicates that BPA can lead to adverse health effects. Increased risk of mortality was observed in a Cohort study that monitored BPA levels 8761 adults over a period of 80,564 person-years. A total of 985 individuals passed away, 314 from cardiovascular disease and 214 from cancer.24

In order to understand the carcinogenic effects of BPA on humans it is important to know how this chemical interacts with the tissues on a molecular level. BPA's pathophysiology in relation to cancer involves a complex interplay of molecular mechanisms that impact various facets of cancer development and progression. Bisphenol A (BPA) is a synthetic compound with distinct structural characteristics. Its chemical structure consists of a central biphenyl core with two hydroxyl (OH) groups and a methyl (CH3) group, which contributes to its estrogenic properties. BPA mimics estrogen and to estrogen receptors α and β (ERα and ERβ), affecting the expression of genes that respond to estrogen.25,26 BPA binds to the ER-related receptor γ (ERR-γ) in addition to ER-α and ER-β.27 BPA also triggers the expression of certain genes in cancer cells associated with cell growth and migration by activating the G protein-coupled estrogen receptor 1 (GPER) signaling pathway.28 Additionally BPA causes reduction in overall DNA methylation, alterations in the structure and chemical marks on DNA-packaging histone proteins, and shifts in the methylation patterns of specific gene-regulating regions. These epigenetic shifts can disrupt the normal control of gene activity, potentially contributing to health concerns, particularly an increased risk of cancer.29-32 Studies showing changes in the proliferation, invasion, growth, migration, and apoptosis of cancer cells have also linked BPA exposure to a pro-carcinogenic impact.33-36

Both in vivo and in vitro studies have identified BPA as a carcinogenic compound; however there is debate among scientists over the safety of BPA and different national agencies are pursuing varied risk management measures. To investigate the potential relationship between Bisphenol A (BPA) exposure and human cancers we conducted a comprehensive systematic literature review. The objective of this literature review is to examine the existing body of evidence on the carcinogenic potential of Bisphenol A (BPA) exposure on humans. By analyzing the available data, this study aims to provide a thorough understanding of the potential associations between BPA exposure and cancer in the human population, contributing to a more holistic assessment of the health risks posed by BPA. Ultimately, the goal is to provide guidance for future research directions in this critical area of environmental health.

**METHODS**

The PICO framework for this review comprised of The human population (P) was the central focus, and the exposure (I) to bisphenol A (BPA) was examined, with a comparison drawn to individuals with no or very low BPA exposure (C). The primary outcome of interest was the prevalence, incidence, mortality or risk of developing various types of cancer (O) in the participants across the selected studies. This structured approach facilitated a comprehensive investigation into the potential association between BPA exposure and cancer development in human populations, contributing essential insights to the field of environmental health and oncology.

The inclusion and exclusion criteria were thoughtfully formulated to guide the systematic review process, ensuring that the selected studies align with the research's primary objective of investigating the connection between BPA exposure and human cancer. All studies that accessed the association between bisphenol A and human cancers were included, provided that BPA exposures were measured. Selected studies had to be peer-reviewed and published in academic journals, upholding rigorous academic standards and enhancing the credibility of the included research. Both in vitro and in vivo human studies were included to ensure a comprehensive examination of the subject, capturing controlled laboratory research as well as real-world studies. We excluded all studies primarily conducted on animals. Review articles, meta-analyses, and systematic reviews were also excluded to maintain a primary focus on original research and empirical studies.

The primary databases accessed for information retrieval were PubMed, Google Scholar, and the Hofstra Library Database. A meticulous and well-structured search strategy was meticulously developed, encompassing a set of distinct search terms and synonyms relevant to the research focus. These search terms included phrases like "Bisphenol A and cancer," "BPA exposure and tumors," "BPA exposure and carcinogenesis," "BPA and hormone cancers," "Hormone-mimicking chemicals and cancer," "Endocrine disruptors and cancer risk," and others, ensuring a wide range of relevant literature. The selection process involved a multi-stage screening approach. After initial screening of titles and abstracts 1272 records were excluded. These exclusions were based on reasons such as duplication, irrelevance, and non-human studies. Subsequent screening stages involved a more detailed assessment of papers to align them with predefined eligibility criteria. A total of 39 reports remained eligible after this comprehensive evaluation. However, eight reports were excluded due to specific criteria, resulting in a final selection of 31 studies. The temporal scope of these studies ranged from January 2003 to September 2023, with no language restrictions. The search strategy was most recently applied on October 26, 2023, ensuring the inclusion of the latest research. Additional search terms, such as "BPA-induced cancer" and "Environmental agents and cancer risk," were incorporated to broaden the scope of the search strategy and gather the most pertinent literature for the review.

In conducting a comprehensive risk bias assessment of the selected studies, various critical aspects were addressed. The focus was on potential selection bias, particularly relevant in case-control and nested case-control studies, where the review rigorously examined methods for identifying and recruiting cases and controls or exposed and unexposed individuals, assessing whether strategies were implemented or not to minimize the risk of selection bias. In addition to these sources of bias, the review critically assessed the measures taken to control confounding factors. Confounders are variables that can distort the relationship between exposure and outcome. Ensuring that the studies adequately controlled for potential confounders, such as age, gender, and lifestyle factors, was imperative for minimizing the risk of bias and obtaining a more accurate evaluation of the associations between exposure and outcomes. The review also examined attrition bias, focusing on data completeness and potential bias due to missing information. It also assessed selective reporting of outcomes to ensure alignment with pre-specified goals and transparent reporting of all relevant data, identifying any disparities between planned and reported outcomes. The potential for information bias, which results from measurement errors or misclassification of data, was also an essential consideration. The review closely examined how the studies measured exposure and identified cases, ensuring that their methods were precise and reliable. Lastly, publication bias was taken into account. This type of bias can occur when studies with significant findings are more likely to be published, leading to an overestimation of the association between BPA exposure and cancer. Efforts were made to explore the potential for publication bias and its impact on the overall conclusions of the review.

**Fig 1. PRISMA flowchart for literature search and study selection**

**Identification of studies via databases and registers**

Records removed *before screening*:

Duplicate records removed (n = 364)

Irrelevant (n =120)

Non-Human studies (n = 524)

1272 Records identified from:

- PubMed: 601

- Google Scholar: 543

- Hofstra Library Database: 128

**Identification**

Records screened

(n =264)

Records excluded (n = 148)

Reports excluded (n = 77)

Reports sought for retrieval

(n = 116)

**Screening**

Reports excluded:

In vitro studies with no association evaluated (n =3)

No statistical analysis (n = 5)

Reports assessed for eligibility

(n = 39)

Studies included in review

(n = 31)

**Included**

**Fig 2. Study Characteristics & Findings**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Region** | **Study Design** | **Study Duration** | **Study Subject** | **Age in Years** | **Sample** | **Exposure Assessment** | **Cancer Type** | **Findings** |
| Salamanca-Fernandez et al. (2021) | Spain, EPIC | Case-Cohort | 1992-2013  (16.9 years follow up) | Females;  547 Cases;  1918 subcohort  Males;  575 Cases  1772 subcohort | 29 - 69 | Blood | Free & Conjugated BPA  DLLME and UHPLC-MS/MS | Breast Cancer  Prostate Cancer | They grouped people into three categories based on their BPA levels.  40% higher risk of prostate cancer in the group with the lowest BPA levels compared to those with undetectable levels.  The middle and highest BPA groups also had increased risks of 37% and 31%, respectively, though these were not statistically significant.  There was no significant link between BPA levels and the risk of breast cancer. |
| Wu et al. (2021) | Hawaii & California | Nested Case-Control | 1993-2014  (1993-1996 enrollment period)  (13 years follow up) | 2062 Females;  1032 Cases  1030 Controls | 45 - 75 | (2001-2006)  Blood  Urine | LC/HRAM-MS | Breast Cancer | Odds ratio  (T2) of BPA exposure: 0.84 (95% CI: 0.67–1.06) indicating a 16% reduction in risk.  (T3) of BPA exposure: 0.95 (95% CI: 0.75–1.21) signifying a 5% reduction in risk  The P-value for the trend was 0.53, indicating that there was no significant trend of increasing or decreasing risk with higher levels of BPA exposure. |
| Morgan et al. (2017) | US  NHANES | Cross-Sectional | NHANES data 1999-2004 | 2007 Female  Participants | 20 - 85 | Urine | LC-MS | Breast Cancer | No significant associations was found between BPA and breast cancer risk |
| Keshavarz-Maleki et al. (2021) | Iran (Tehran) | Case-Control | July 2018 to December 2019 | 52 Females;  41 cases;  Mastectomy patients  11 control;  Reduction mammoplasty patients. | 34 - 72 | Urine  Breast Adipose tissue | ELISA kit (Detroit R&D) | Breast Cancer | BPA levels in cases  92.68% - urine  73.17% - adipose tissue  BPA levels in controls  81.82% - urine  73.17% - adipose tissue  BPA levels in urine and tissue were significantly higher in the breast cancer (case) group than in the control group.  The presence of BPA in breast adipose tissue might increase the risk of breast cancer incidence |
| Hiroi et al. (2004) | Japan | Cross-Sectional | NA | 37 Females;  10 - SEH  9 - CEH  11- Endometrial cancer  11 Controls | 40-56  for SHE, CEH & Controls  58-68 for cancer | Blood | ELISA | Endometrial Cancer | BPA in the blood were lower in patients with complex endometrial hyperplasia and endometrial cancer when compared to normal women and those with simple endometrial hyperplasia. |
| Tarapore et al. (2014) | US  (Cincinnati) | Cross-Sectional | NA | 60 Males;  27 Cases  33 Controls | Case;  56-87  Control;  46-77 | Urine | HPLC coupled with ESI-MS/MS | Prostate Cancer | BPA levels in PCa patients were approximately 300% higher (5.74 / 1.43 = 4) than those in non-PCa patients.  In the group of patients under 65 years of age, PCa patients had BPA levels approximately 800% higher (8.08 / 0.90 = 8.9) than non-PCa  These findings suggest a significant association between higher BPA levels and the presence of prostate cancer. |
| Aquino et al. (2019) | Italy | Pilot Case- Control | December 2016 to May 2017 | 24 Females;  17 Cases  7 Controls | 50 - 69 | Urine  Blood  Uterine tissue | Free & Conjugated BPA  GC-MS/MS | Endometrial Cancer | Total BPA was 39% higher in the blood and urine of women with endometrial cancer (cases) compared to women with benign uterine conditions (controls).  Total BPA in uterine tissue were 69% lower in cases compared to controls. |
| Hong et al.  (2022) | China | Case Control | July 2017 to October 2019 | 122 Males;  50 Cases  72 Controls  95 Females;  37 Cases  58 Controls | Case;  49 - 72  Control;  48 - 73 | Urine | LC-MS/MS | Colorectal Cancer | * BPA detection rate in CRC patients: 88.5% * Median urinary BPA concentration in CRC patients: 1.92 µg/g * BPA detection rate in healthy controls: 93.8% * Median urinary BPA concentration in healthy controls: 1.65 µg/g   They divided CRC patients into high and low BPA exposure groups based on a cut-off value of 4.21 μg/g.  In the high exposure group, participants were more likely to have:   * Larger tumor sizes. * Higher degrees of pathological infiltration stage. * Longer transfer distances. * Higher differentiation grades (all with P < 0.05).   A significant positive association between BPA exposure and the risk of colorectal cancer, particularly in individuals with higher BPA exposure levels. |
| Tse et al. (2017) | China  (Hong Kong) | Case-Control | August 2011 and November 2016 | 833 Males;  431 Cases  402 Controls | 35–84 | Self-reported use of food & beverage container | Cumulative BPA Exposure Index  (CBPAI) | Prostate Cancer | Only 7 (1.6%) cases and 1 (0.2%) control had incomplete information on BPA.  There was a positive exposure-response relationship between CBPAI and prostate cancer, |
| Loperz-Carrillo et al. (2021) | Northern Mexico | Case-Control | 2007 to 2011 | 798 Females;  394 Cases  404 Controls | Median age of 52 years | Urine | Biologically active form of BPA (BPA-F)  HPLC/FLD | Breast Cancer | The levels of BPA-F (a form of BPA in urine) were significantly higher in cases compared to controls (3.16 μg/L in cases and 2.47 μg/L in controls)  Breast cancer was significantly associated with BPA-F levels, particularly among women with the highest BPA-F exposure compared to those with the lowest. |
| Trabert et al. (2014) | Poland | Case-Control | January 2000 - January 2003 | 1150 Females;  575 Cases  575 Controls | 20–74  (mean = 59) | Urine | Unconjugated BPA & BPA-G  HPLC/MS/  MS | Breast Cancer | There was no indication that increased BPA-G was associated with post-menopausal breast cancer (p-trend = 0.59) |
| Ajayi et al. (2014) | Nigeria | Case-Control | NA | 80 Females;  40 Cases  40 Controls | Cases; 47.90 ± 1.83  Control; 51.10 ± 2.32 | Blood | Solid-phase extraction with HPLC | Breast Cancer | BPA levels were significantly higher in breast cancer patients, indicating it might play a role in breast cancer development. (p<0.05) |
| Ishtiaq et al. (2023) | Pakistan  (Rawalpindi,) | Cohort | NA | 45 breast cancer patients | NA | Breast Tissue  Blood | HPLC–UV | Breast Cancer | Use of canned food;  4.7% Yes  95.2% No  Use of plastic bottles;  71.4% Yes  28.5% No  The level of BPA in the serum samples of breast cancer patients was significantly higher than control |
| Zhang et al. (2023) | China | Case-Control | June 2017 to September 2017 | 172 Females;  86 Cases  86 Controls  50 Males;  25 Cases  25 Controls | 42.5 ±  11.2 | Urine  Blood | UPLC-MS/MS | Papillary Thyroid Cancer | BPA had the highest average concentration, followed by BPF and BPS.  Higher levels of BPF were associated with an increased risk of PTC (odds ratio of 1.80), while higher levels of BPA and BPS were associated with a decreased risk of PTC (odds ratios of 0.38 and 0.63, respectively). |
| Marotta et al. (2023) | Italy | Cross-Sectional | May 2017 to May 2019 | 96 participants;  41 Cases;  55 Controls;  (30 Males,  66 Female) | Median age 51  (19–77) | Blood | HPLC | Thyroid Cancer | Subjects with benign nodules as control group  In the overall study population and in the group with BMI<25 kg/m2 BPA exposure was not significantly correlated to thyroid cancer (p = 0.08)  In the group with BMI≥25 kg/m2, BPA-exposed subjects showed significantly higher risk of malignancy (= 0.028).  BPA exposure is a risk factor for thyroid cancer in overweight/obese subjects**.** |
| Deng et al.(2021) | China  (Wuhan) | Case- Control | November 2016 to October 2019 | Females;  105 Cases;  179 Controls;  Males;  170 Cases;  358 Controls; | Cases 59.22 ± 11.22,  Controls 58.80 ± 8.08 | Urine | UHPLC with MS | Colorectal Cancer | BPA was detected in nearly all samples among cases and controls, indicating people had widespread exposure to BPA.  The observed urinary concentration of BPA in cases was significantly higher compared with controls.  BPA is associated with Colorectal Cancer risk |
| Zhou et al. (2017) | China | Case- Control | February 2013 to September 2013 | 113 Cases;  53 PTC  60 NG (Nodular Goiter)  65 Controls’  (Females 128  Males 50) | NA | Blood  Urine | Total (free & conjugated) BPA  HPLC–MS/MS | Papillary Thyroid Cancer (PTC) | There were no differences in serum total BPA concentration among the NG, PTC, and the healthy control groups  Urinary BPA concentrations (UBC) were higher in the NG and PTC groups compared with the control group  High UBC, but not serum total BPA concentrations (TBC), are likely to be associated with NG and PTC |
| Yang et al. (2009) | South Korea | Case- Control | 1994 - 1997 | 152 Females;  70 Cases;  82 Controls; | Case;  46.23 ± 10.39  Control;  48.56 ± 11.69 | Blood | Free & conjugated BPA  Reverse phase-HPLC/FD & LC/MS/MS | Breast Cancer | In age-matched subjects (*N* = 152), there were some associations between BPA levels and risks of breast cancer, such as age at first birth and null parity.  However, there were no significant differences in blood BPA levels between the cases and the controls (*P* = 0.42).  This suggests that the Korean population may have slightly lower exposure to BPA compared to some other regions. |
| Bao et al. (2020) | US, NHANES | Cohort | 2003–2015  Person-years of follow-up  (Median, 9.6 years;  Maximum, 13.1 years) | 3883 participants  (both sexes) | >20 | Urine | Solid-phase extraction & HPLC with MS/MS | All Cancer Types | During 36 514 person-years of follow-up 75 deaths occurred from cancer.  After adjustment for age, sex, race/ethnicity, and urinary creatinine levels, participants higher urinary BPA levels had a 51% higher risk of all-cause mortality  There was no statistically significant association between BPA exposure and cancer mortality. (HR, 0.98; 95% CI, 0.40-2.39) |
| Morgan et al. (2016) | US, NHANES | Cross- Sectional | 2005 - 2010 | 2202 Females;  (15 cervical, 16 ovarian, & 22 uterine cancer cases) | 20 - 85 | Urine | Solid-phase extraction & HPLC with MS/MS | Cervical,  Ovarian, & Uterine Cancers | BPA levels were elevated in women with ovarian cancer when compared to those without gynecologic cancer.  However, when the analysis was adjusted for various factors such as age, race, BMI, and age at menarche, statistically significant associations was not found between urinary BPA and gynecologic cancers. |
| Morgan et al. (2017) | US, NHANES | Cross- Sectional | 2005 - 2010 | 2145 Females | 20 - 85 | Urine | Solid-phase extraction & HPLC with MS/MS | Breast Cancer | BPA significantly higher in women without cancer vs. women with breast cancer, p < 0.05.  The statistical analysis showed that there was no significant association between BPA levels and breast cancer risk.  The statistical analysis did not show a significant link between BPA exposure and breast cancer, even after adjusting for factors like age, race, BMI, and age at menarche. |
| Ahrens et al. (2007) | Denmark, France, Germany, Italy, Spain, Sweden | Case- Control | 1995 - 1997 | 183 Cases;  1938 Controls;  For BPA  Exposed;  9 Cases  87 Controls  Unexposed; 114 Cases 1784 Controls | 32 - 72 | Self-reported job  Descriptions | Cumulative Exposure Index (CEI)  (Semi quantitative variables;  1. Probability  2. Intensity  3. Duration of exposure) | Biliary Tract Cancer | In this study, the risk of extra hepatic biliary tract cancer was increased among the participants ever exposed to endocrine-disrupting compounds with a known estrogenic effect (alkyl phenols, PCB, bisphenol A). |
| Marotta et al. (2019) | Italy | Cross- Sectional | 2017 | 55 participants;  28 - DTC  27 - benign nodules  (Both sexes) | 15–77 | Blood | HPLC/FD/  UV | Differentiated Thyroid Cancer (DTC) | A significant correlation between human exposure and the risk of DTC was found for 2 BPs (BPE and BPAF) (OR 14.44, 95% CI 11.69–122.98, p= 0.005)  A significant relationship was found between malignancy and the detection in the serum of both bisphenol AF |
| Qu et al. (2022) | China | Case- Control | January 2020 –  May 2021. | 226 Cases;  243 Controls;  (269 Males, 200 Females) | 31 - 78 | Urine | BPA, BPS & BPF  UPLC-MS/MS | Lung Cancer | BPA and BPS concentrations were higher in the case group, while BPF concentrations were similar in both groups.  In the stratification analysis, the significant correlation between urinary creatinine-corrected concentrations of BPA and the risk of lung cancer still observed in male participants (OR = 1.36, 95% CI: 1.09, 1.62, *p* = 0.040).  This study demonstrates that elevated human exposure to BPA and BPS may be associated with the increased lung cancer risk. |
| Chen et al. (2022) | China | Case- Control | March - December 2016 | 143 Cases;  224 Controls;  (264 Females, 103 Males) | NA | Urine | BPA, BPS, BPF  UPLC coupled to quadrupole mass spectrometry (MS/MS) | Thyroid Caner | Among the measured phenols, BPS had the highest detection rate, followed by BPA, and BPF had higher detection rate in the control group than that in the cancer group,  It was found that elevated urinary bisphenol A (BPA) and bisphenol S (BPS) levels were associated with increased risk of thyroid cancer (all *P* for trends < 0.05) |
| li et al. (2020) | China | Case- Control | 2016 - 2018 | 615 Cases;  615 Controls;  (Both sexes) | Cases;  59.2 mean  Control;  58 mean | Urine | Total BPA  UHPLC/MS | Non-Small Cell Lung Cancer (NSCLC) | NSCLC cases had higher urinary BPA levels when compared to the healthy controls.  The positive associations between BPA concentrations and NSCLC were significant in both males (*P* = 0.001 for the highest quartile) and females (*P* = 0.021 for the highest quartile).  Exposure to high levels of BPA was significantly associated with NSCLC (adjusted OR = 1.91, 95%CI: 1.39–2.62, *P* < 0.001 for the highest quartile). |
| Parada et al. (2019 | US | Case- Control | 1996 – 2014 | 711 Cases  598 Controls | 22 - 96 | Urine | Solid-phase extraction with HPLC & MS/MS | Breast Cancer | BPA levels were elevated in some women with breast cancer, but the statistical significance of this finding was not very strong.  Further research may be needed to better understand the relationship between BPA exposure and breast cancer. |
| Jia et al. (2013) | China | Case- Control | 2009–2011 | 106 Cases; 112 Controls;  Both sexes | 16.13 ± 2.80 Cases  15.89 ± 2.13 Controls | Urine | HPLC-MS | Osteosarcoma | The study suggested that -22G/C polymorphism in LOX gene may have modified the relationship between BPA exposure and osteosarcoma risk.  High BPA exposure was associated with an increased risk of osteosarcoma overall |
| Shivam et al. (2022) | India | Case- Control | NA | 45 Cases  45Controls | 18 - 75 | Blood | Structural changes in blood components by BPAQ using UV visible Spectrophotometry | Breast Cancer | The serum samples from breast cancer patients had increased mean absorbance at a range of 250 nm to 300 nm and 360 nm to 450 nm as compared to control samples  The results revealed that there is an association between active metabolite of Bisphenol-A and MDM2 SNP309 G variant with the risk of breast cancer in Indian population. |
| Komarowska et al. (2022) | Poland | Pilot Study | NA | 53 participants  24 - low grade meningioma  29 – glioma  (27 Females, 26 Males) | 20 - 71 | Plasma | Free & Conjugated BPA  GC-MS | Meningioma & Glioma | The concentrations of BPA in patients were compared to those obtained in wide-ranging studies published in the literature.  Free and conjugated BPA were present in both meningioma and glioma patients. Moreover, their concentrations far exceeded those reported in the healthy population.  Occurrence of both meningioma and glioma may be accompanied by increased concentrations of leptin and BPA.  Further large-scale studies are needed to clarify whether the presence of both substances may play a role in pathogenesis or influence clinical course in patients with brain neoplasms. |
| **Duan et al. (2013)** | China | Case- Control | 2009-2010 | 45 Cases  45Controls | 53.5 Cases  54.7 Controls | Urine | Total BPA  Solid-phase extraction coupled with HPLC–MS | Meningioma | Increasing urine BPA levels are positively associated with meningioma (*P* < 001, OR = 1.4, 95 % CI = 1.1 ≤ OR ≤ 1.8).  The association between BPA and meningioma did not differ by BMI status. |

Notes: BPA = Bisphenol A; BPA-G = BPA-Glucuronide; CBPAI = Cumulative BPA Exposure Index; ELISA = Enzyme-Linked Immunoassay; FD = Fluorescence Detector; GC = Gas Chromatography; HPLC = High-Performance Liquid Chromatography; LC = Liquid Chromatography; MS = Mass Spectrometry; MS/MS = Tandem Mass Spectrometry; NA = Not Available; NHANES = National Health and Nutrition Examination Survey; UHPLC = Ultra-High-Performance Liquid Chromatography; UPLC = Ultra-Performance Liquid Chromatography; US = United States; UV = Ultraviolet.

**RESULTS**:

Figure 2 lists the characteristics and results of the 31 studies included in the literature review. The main findings are briefly explained below.

Studies investigating the potential link between Bisphenol A (BPA) exposure and cancer outcomes span the globe, with a focus on China (10 studies) and the United States (7 studies). 6 studies were based in European countries. Additionally, 8 studies included a range of regions i.e. Nigeria, Iran, Mexico, Japan, South Korea, Pakistan, Northern Mexico, and India. The diverse geographic representation indicates a global interest in understanding the relationship. Moreover, the variety in study designs reflects a comprehensive approach to investigating this association, considering different methodologies to enhance the robustness of the research findings. The preeminent choice appears to be the case-control approach, elegantly employed in 20 studies. Seven studies adopt a cross-sectional design, followed by 3 Cohort, and 1 pilot study.

The participant statistics in the 31 included studies showed considerable variability in sample sizes, ranging from 24 participants in an Italian study**37** to 3,883 participants in an NHANES-based study.**38** The duration of the studies also varied considerably, ranging from a few months to several years. The longitudinal aspect of the studies was limited as only three studies reported the follow-up period with the participants, which were 16.9 years, 13 years, and 9.6 to 13.1 years respectively. However, these studies did not mention how frequently they did so. The other studies that mentioned their duration did not specify if they followed up the participants. Moreover, the sample was collected only once in all the studies.

The studies on BPA exposure and cancer covered a range of cancer types, with breast cancer being the most frequently investigated (11 studies). Thyroid cancers were also relatively common (5 studies). Prostate, colorectal, endometrial, and lung cancers each had 2 studies, while meningioma, biliary tract, osteosarcoma, and gynecological cancers (including cervical, ovarian, and uterine cancers) each had 1 study. One study examined both breast and prostate cancers simultaneously, while another study evaluated all cancer types together. Glioma and meningioma were combined in one study.

The outcome variables were the incidence, prevalence, or mortality of different cancers. The majority of the studies confirmed the cancer diagnosis by histopathological examination of tissue samples obtained from surgery or biopsy. Some studies also validated the cancer outcomes by mammography, ultrasonography, clinical examination, medical records, biomarkers, or the National Death Index and the state vital statistics. Only one study did not confirm the cancer diagnosis by any biomarkers or medical records, but relied on the self-report of the participants.**39**

Out of these 31 studies, 20 reported a positive association, suggesting a potential link between BPA exposure and cancer. However, 10 studies found no such association, highlighting conflicting evidence in the literature. One study presented a mix of associations, further adding complexity to the overall findings. Delving into cancer-specific investigations, breast cancer exhibited a divided outcome, with 5 studies supporting an association and 6 reporting no association. Noteworthy findings were observed in thyroid studies, where 4 studies indicated an association, emphasizing a potential impact of BPA on hormone-related cancers. Positive associations were also evident in studies related to lung cancer, osteosarcoma, meningioma, glioma, biliary tract, prostate, and colorectal carcinoma. However, endometrial studies provided contrasting results where one study found an association and the other did not. The study evaluating all cancer types found no association. Similarly, the examination of gynecological cancers did not reveal an association. A mixed finding emerged from the study simultaneously evaluating both prostate and breast cancers, which showed an association only with prostate cancer.

One of the aspects of studies that needs more attention is the disparity in the number of studies focusing on general population vs. occupational exposure. Only one study has specifically investigated this occupational exposure among workers. The authors measured the lifetime exposure to BPA and other EDCs for each participant based on their self-reported job descriptions. They converted the job descriptions to semi quantitative variables (intensity, probability, and duration of exposure) for each exposure. The Cumulative Exposure Index (CEI) was calculated for each EDC by multiplying the intensity, probability, and duration of exposure for each job and summing them over the lifetime.**40** One more study relied on self-report data to access BPA exposure levels among participants. A questionnaire was used to collect information on the participants’ demographic characteristics, medical history, lifestyle factors, and dietary habits. They also asked about the regular use of certain food or beverage containers that may contain BPA, such as plastic bottles, metal cans, and polycarbonate cups. Based on the frequency and duration of use of these containers, a cumulative BPA exposure index (CBPAI) was calculated for each participant. It was found that the cases had a significantly higher CBPAI than the controls (mean = 3.4 vs. 2.8, p < 0.001).**41**

The most common type of human sample is urine, which was used in more than half of the studies (n=15). Blood was the second most common type (n=7), followed by a few studies that used both urine and blood (n=3). Some studies also used other types of samples, such as breast tissue (n=2), uterine tissue (n=1), and plasma(n=1). The most common technique for measuring BPA is liquid chromatography-tandem mass spectrometry (LC-MS/MS), which can detect both free and total BPA. Some studies have also used gas chromatography-mass spectrometry (GC-MS) or enzyme-linked immunosorbent assay (ELISA) to measure the serum levels of BPA. Additionally, some studies have examined the genetic variants or gene expression profiles of genes related to BPA metabolism or thyroid hormone function by using microarray technology or polymerase chain reaction (PCR). The exposure measurement methods vary depending on the type and number of phenols, the biological samples, and the analytical instruments used in each study.

Six studies additionally reported that BPA was involved in tumor aggressiveness. The levels of BPA and its analogues (BPF and BPS) in urine and serum were higher in patients with more advanced and aggressive tumors, regardless of the type of cancer. The tumor aggressiveness was measured by various indicators, such as tumor size, lymph node involvement, hormone receptor status, molecular subtype, Gleason score, clinical stage, PSA level, extrathyroidal extension, and BRAF mutation.**41-46**

The form of BPA being measured was reported only in 12 studies out of the total. Four of these studies measured both free and conjugated BPA, while two studies measured total BPA only. Two other studies also measured BPS and BPF along with BPA. One study evaluated BPAQ, which is a metabolite of BPA. Another study measured total, free and conjugated BPA separately. One study focused on unconjugated BPA and BPA-G, which are also metabolites of BPA. The last study measured the biologically active form of BPA, which is BPA-F.

The studies applied various methods to account for the confounding factors that could influence the relationship between BPA exposure and different health outcomes. The most frequent methods were multivariate logistic regression models, conditional logistic regression models, Cox proportional hazards models, analysis of covariance (ANCOVA), and multiple linear regression (MLR) models. The confounding factors that were adjusted for varied across the studies, but some of the most frequent ones were age, sex, body mass index (BMI), smoking status, alcohol consumption, education level, family history of cancer, and hormone therapy use. Some studies also adjusted for other factors, such as dietary intake, physical activity, urinary creatinine, and history of cholelithiasis. One study, however, did not adjust for the confounding factors that could affect the levels of BPA in the body, such as diet, lifestyle, environmental exposure, or genetic variation, and recognized this as a limitation**.47** The studies acknowledged the limitations of their methods and the possibility of residual confounding.

**DISCUSSION**:

The literature review conducted in this study aimed to evaluate the association between bisphenol A (BPA) and cancer in humans. The results showed that the existing evidence is mixed and inconclusive due to several limitations in these studies.

The sample size of each study is indeed an important factor that affects the quality and precision of the evidence. A larger sample size can increase the statistical power and reduce the sampling error of the study, which can improve the accuracy and reliability of the results. A smaller sample size, on the other hand, can decrease the statistical power and increase the sampling error of the study, which can lead to false positives or false negatives in the results.While these studies contribute valuable insights into the associations between Bisphenol A (BPA) exposure and various health outcomes, the diversity in participant numbers raises challenges in generalizing the findings to the entire world population. Smaller studies may provide important preliminary information, but their limited sample size raises concerns about their representativeness and statistical power. For instance, most of the studies with relatively smaller cohorts found an association**.37,47-49** However, it's crucial to recognize that these results might be influenced by factors like chance, bias, or limited statistical power due to the smaller sample sizes. Contrastingly, most of the studies with larger participant size mainly those with more than 1500 participants showed a trend towards no association between BPA and cancer.**50-52** The fact that larger studies generally lean toward no association raises questions about the strength and consistency of the observed associations in smaller studies. While smaller studies can provide valuable insights, caution is needed in generalizing their findings, as the observed associations may be more susceptible to chance. Having a small sample size can lead to biased results. This is because the sample may not be representative of the population, which can lead to overestimation or underestimation of the true effect.

The temporal dimension was also limited in several ways. Firstly, the duration of the studies varied considerably, ranging from a few months to several years. This may introduce heterogeneity and bias in the comparison of the studies, as different durations may capture different levels of exposure. Second, the longitudinal aspect of the studies was limited as only three studies reported the follow-up period with the participants. However, these studies did not mention how frequently they followed up the participants. The other studies that mentioned their duration did not specify if they followed up the participants. This may affect the reliability and accuracy of the data, as the participants may have changed their exposure or lifestyle habits over time, or may have been lost to follow-up or died. Furthermore, the lack of follow-up may also miss the potential confounding or modifying factors that may influence the association between BPA and cancer.

Another flaw is the lack of temporal relationship between BPA exposure and cancer development. Most of the studies used cross-sectional or case-control designs, which can only measure the exposure and outcome at the same time or retrospectively. This makes it difficult to determine whether BPA exposure preceded or followed the cancer diagnosis, or whether they occurred simultaneously. Moreover, these designs cannot account for the potential reverse causation, where cancer may affect the levels of BPA in the body rather than the other way around. For example, cancer patients may have altered hormone levels, immune function, or metabolism, which may influence the clearance or accumulation of BPA in the body.**53** Therefore, the studies that used cross-sectional or case-control designs may have confounded the association between BPA and cancer by ignoring the temporal sequence of events.

The use of self-report methods in some studies to evaluate for the confounding factors, exposure assessment and cancer diagnosis also introduces several potential flaws that may compromise the validity and reliability of the findings. Self-report methods lack the ability to capture a comprehensive picture of overall exposure, as individuals are exposed to BPA through various sources. This can introduce measurement bias, as the participants may not remember or report accurately their exposure to BPA through their occupation, diet, or use of food containers. Moreover, self-reported data may not reflect the actual levels of BPA in the body, as there are many factors that can influence the absorption, distribution, metabolism, and excretion of BPA, such as genetic variation, diet, lifestyle, medication use, or environmental exposure. The use of self-report method to adjust for confounding factors can affect the reliability of reported data. Self-report methods are also prone to recall bias, information bias, misclassification bias, and selection bias, which can result in inaccuracies and distortions in the measurement and classification of key study variables. Self-report methods may not capture the full spectrum of the outcome variable, such as the type, stage, or severity of cancer. These limitations may affect the internal and external validity of the studies, reducing their ability to draw firm conclusions about the relationship between BPA exposure and cancer outcomes.

One of the main sources of heterogeneity in the literature is the collection human biological samples only once throughout the study period and the different methods of BPA exposure assessment. BPA exposure can be measured by various biomarkers, such as urine, blood, saliva, breast milk, amniotic fluid, or placenta. However, these biomarkers may reflect different windows of exposure, different forms of BPA, and different levels of contamination or degradation.**54** Moreover, the timing of sample collection may influence the BPA level detected, as BPA has a short half-life.**55** Additionally, BPA exposure can vary greatly over time and across individuals, depending on the dietary intake, environmental exposure, and metabolic clearance of BPA.**56** Therefore, different biomarkers and different times of sample collection may provide different estimates of BPA exposure in the human body. Urine samples are the most commonly used type of human sample in these studies for BPA measurement, probably because they are easy to collect and store, and they reflect the recent exposure to BPA. Urine samples can capture the peak levels of BPA and its metabolites after ingestion, which usually occur within a few hours.**57** However, urine samples may not be an accurate indicator of the internal dose of BPA in the body and may not reflect the chronic or long-term exposure to BPA, because the levels of BPA and its metabolites in urine can vary depending on the hydration status, diet, and time of collection.**58** Blood samples are another way BPA measurement, but they are less frequently used, because they are more invasive and difficult to collect and store. Blood samples can reflect the longer-term exposure to BPA, because BPA and its metabolites can bind to proteins and lipids in the blood, and circulate in the body for longer periods of time.However, they may be influenced by factors such as blood volume, blood flow, and metabolism.**59,60** Therefore, a single or spot measurement of BPA as done in these studies may not capture the true exposure level or the cumulative dose of BPA over the relevant period of carcinogenesis.

One of the useful methods for monitoring BPA exposure and bioaccumulation in humans is sweat analysis. Sweat analysis can detect BPA levels that may not be found in blood or urine samples, and it can also help to eliminate BPA from the body through induced sweating. This method was proposed by a study that found BPA in the sweat of 16 out of 20 participants, even in some individuals with no BPA detected in their serum or urine samples. Sweat analysis should be considered as an additional method for monitoring bioaccumulation of BPA in humans, as blood and urine testing may underestimate the total body burden of this potential toxicant.**61**

BPA has different forms that can affect the body in different ways. The free monomer is the most estrogenic form, but the glucuronide form can also cause obesity by activating PPARγ 3. The glucuronide form is the main way that BPA is metabolized in humans, but it can be turned back into the free monomer by bacteria in the gut 1. This means that the effects and metabolism of BPA depend on how much, how often, and how it is exposed, as well as the individual differences in the body 2. The form of BPA that is measured and the tissue or organ that is affected may also change the dose-response relationship of BPA. This makes it hard to assess the risk of BPA exposure and requires more research to understand how BPA works in different forms.**62-64**

Depending on the type of sample, the method of analysis, and the study goal as employed in these investigations, there may be differences in the optimal approach to quantify BPA levels in human biological samples. However, a new report in The Lancet Diabetes & Endocrinology shows that a new direct mass spectrometry method without enzyme deconjugation can detect BPA levels in humans that are up to 44 times higher than the average amounts reported by national health surveys. The new method measures BPA, BPA glucuronide, and BPA sulfate directly. The researchers compared the results from their new direct method with the results from indirect methods used by the CDC and the FDA on synthetic urine with added BPA, and then tested 39 human samples. The new direct method found much higher levels of BPA—more than 44 times the average amount reported by NHANES. It is important to note that BPA breaks down quickly in the body, forming chemical products called “metabolites,” which makes it hard to test for in blood or urine in its original form 1. However, the new direct method without enzyme deconjugation offers a way to check the accuracy of the indirect methods that are widely used.**65-67**

There is also lack of data from consumer products that provides evidence that BPA causes cancer in humans. Especially when it has proposed that food and drink containers are the primary source of human BPA exposure. And that consumption of canned soup for 5 days can results in a 1200% increase in urine BPA compared to fresh food.**68**

There has been a ton of research published on the hormonal activity and toxicity of BPA in lab animals. Regarding both the type of the effects seen and the levels at which they occur, there have been significant differences in these research' findings. As a result, there is debate among scientists over the safety of BPA, and different national agencies are pursuing varied risk management measures. The widespread use of BPA and the adverse effects on development and reproduction seen in animal studies have drawn a lot of attention to this chemical in recent years. However, the evidence for BPA as a carcinogen in humans is not conclusive, as most of the studies have been conducted in vitro or in animal models, and the results are not consistent or reproducible across different experimental settings and doses. Animal models that have been used extensively in the literature to assess the health consequences of BPA do not lend to reach conclusions regarding a potential risk for humans, as there are multiple drawbacks in these studies. The doses of BPA used in animal studies are often much higher than the levels that humans are exposed to through food and other sources. One study found that rats exposed to BPA at doses of 2.4 mg/kg/day or higher developed mammary tumors, while the estimated daily intake of BPA for humans is around 0.004 mg/kg/day.**69** Another research on animals to evaluate the negative effect of BPA on the kidney and liver revealed the effects to be evident at high doses (more than 100 times the TDI) which exceeds the daily EDI in humans.**70** An additional investigation into the carcinogenicity of BPA from an animal study revealed that while a statistically significant increase in testicular interstitial-cell tumors in male rats was suggestive of carcinogenesis, it was not considered substantial evidence of a compound-related effect because these lesions frequently develop in older F344 rats.**71** The genetic and environmental factors that influence the response to BPA in animal studies may not be representative of those in humans. Animal studies usually use inbred strains of rodents that have a high degree of genetic homogeneity, while humans have a high degree of genetic diversity and variability. Moreover, animal studies are conducted under controlled laboratory conditions, while humans are exposed to multiple environmental factors and stressors that may modulate the effects of BPA. Animal models may not accurately reflect the human physiology, metabolism, and exposure scenarios of BPA. A study found that mice exposed to BPA during pregnancy had increased mammary gland tumors in their offspring, but this effect was not observed in monkeys exposed to the same dose of BPA. This suggests that different species may have different responses to BPA exposure.**72** Studies have shown that humans, rats, and mice process BPA differently. In humans, the liver seems to have a greater capacity for turning BPA into its glucuronide form, which aids in its elimination from the body, especially after oral exposure. Therefore, while animal studies provide valuable insights into the potential mechanisms and effects of BPA on the body, they have some limitations that need to be considered when extrapolating their results to humans.

The current literature does not provide solid evidence that BPA causes cancer in humans, because it lacks reliable and consistent ways to measure BPA exposure and its effects. BPA is quickly broken down and removed from the body through urine, so the levels of BPA in blood or tissues may not show the real exposure or the risk of harm. Moreover, different studies use different methods and criteria to assess BPA exposure, such as self-reported questionnaires, food frequency surveys, or spot urine samples, which may introduce bias and variability in the results. Additionally, BPA can interact with other environmental or genetic factors that may modulate its effects on the endocrine system and cancer risk. Even though most of the confounders were adjusted, there may still be other unmeasured confounders that are often not accounted for or controlled in the studies. These unmeasured confounders may have biased the association between BPA and cancer by either exaggerating or attenuating the effect size. The literature is also inconclusive as these studies only reported associations that may be confounded by the unmeasured factors or influenced by chance. Moreover, there is conflicting evidence among these studies to form a strong association. This inconsistency introduces a significant barrier to drawing clear and consistent conclusions**.** Therefore, it is difficult to establish a definitive causal relationship between BPA exposure and the risk of developing cancer in humans.

FDA and other International authorities have used generally recognized approaches to human health assessment and have reached the conclusion that current uses of BPA do not present human health risks necessitating additional regulatory controls. The FDA modified its regulations to ban the use of BPA in infant formula packaging and baby bottles and sippy cups in response to market changes and consumer preferences, not because of safety concerns. The FDA stated that these changes did not reflect a change in its safety assessment of BPA, but rather recognized that the industry had already stopped using BPA in these products. The FDA also noted that these changes would enhance consistency between the U.S. and other countries that have similar bans. FDA has explained that the bans were not based on scientific evidence of harm, but rather on other factors, such as consumer demand and international alignment

To improve the quality and reliability of the evidence on the association between BPA and cancer in humans, future studies should address the limitations of the existing literature, which mainly stem from the limited temporal dimension of the studies. Specifically, future studies should: (a) follow the participants for a longer duration and a more frequent interval, to capture the temporal changes in the exposure and outcome, and to adjust for the effects of time-varying factors; (b) measure the exposure and outcome more accurately and consistently, to reflect the actual exposure over time, and to capture the disease progression or regression over time; (c) sample a more comprehensive and representative population, to include the individuals who may have been exposed to BPA for a longer period of time, and to account for the population heterogeneity and diversity; and (d) design the studies more rigorously and robustly, to control for the potential confounding and biasing factors, and to establish the causal relationship between the exposure and outcome.

While traditional methods of detecting Bisphenol A (BPA) levels have primarily focused on urine and blood samples, it has become increasingly important to evaluate additional body tissues, including sweat. This expanded approach is driven by the need for a more comprehensive assessment of BPA exposure. Recent studies have revealed that BPA can be present in sweat, even when it is not detected in urine or serum samples. Relying solely on traditional tests might, therefore, risk underestimating the extent of BPA exposure. By considering a broader range of body fluids and tissues, researchers can gain a more holistic understanding of BPA bioaccumulation in the human body. Furthermore, this approach introduces intriguing possibilities, such as using induced sweating as a potential therapeutic method for BPA elimination, offering new avenues for research into BPA detoxification strategies.

Ideally, BPA exposure should be measured longitudinally and repeatedly, using multiple biomarkers and accounting for the temporal variability and the pharmacokinetics of BPA. However, such methods are costly, invasive, and impractical for large-scale epidemiological studies. Therefore, most of the existing studies rely on a single or spot measurement of BPA, usually in urine, which may introduce measurement error and misclassification bias. Moreover, cancer development is a complex and multifactorial process that involves genetic, environmental, and lifestyle factors. It may take years or decades for cancer to manifest clinically after the initial exposure to a carcinogen. Additionally, BPA may interact with other environmental or genetic factors that may modulate its effects on cancer, such as diet, smoking, alcohol, or family history. Therefore, the effects of BPA on cancer may vary depending on the individual characteristics and the context of the exposure. Future studies should consider these factors and their interactions when examining the effects of BPA on cancer.

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