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Three photoinitiators induce breast tumor growth in mouse xenografts with MCF-7 breast cancer cells

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ABSTRACT

Photoinitiators are utilized in the production of a wide range of commonly used products. However, some photoinitiators exert toxic effects. We previously demonstrated the endocrine-disrupting effects of photoinitiators *in vitro*. The present study investigated the estrogenic activities of three photoinitiators: 1-hydroxycyclohexyl phenyl ketone (1-HCHPK), methyl 2-benzoylbenzoate (MBB), and 2-methyl-4′-(methylthio)-2-morpholinopropiophenone (MTMP), which were subcutaneously injected into mouse xenografts with MCF-7 breast cancer cells. The results obtained showed that 1-HCHPK, MBB, and MTMP promoted breast tumor growth in these xenografts. A pretreatment with the estrogen receptor antagonist tamoxifen blocked the tumor growth-promoting effects of each photoinitiator. Collectively, the present results suggest that the three photoinitiators exhibit estrogenic agonist activities *in vivo*. Furthermore, as a factor for breast tumor growth, these photoinitiators potentially have estrogenic properties *in vivo*.

Introduction

Photoinitiators are utilized in the production of a wide range of commonly used products, including adhesives, items in the printing industry (inks, printing plates), toys (fabrication of 3D objects), and materials in the medical field (dental filling materials and artificial tissues) (Dumanian et al., 1995; Kostoryz et al., 1999; Bohonowych et al., 2008; Santini et al., 2013). Some photoinitiators have been reported to exert toxic effects under *in vitro* conditions (Kostoryz et al., 1999; Eick et al., 2002; Huang et al., 2002; Williams et al., 2005; Demirci et al., 2008). Furthermore, *in vivo* studies demonstrated that the photoinitiator benzophenone, which is present in sunscreen, induced allergic skin reactions, similar to skin irritants that cause photoallergies, allergic contact dermatitis, and facial erythema (Alanko et al., 2001; Cook and Freeman, 2001; Nedorost, 2003). However, the health hazards associated with the different entry routes of photoinitiators into the body and their effects on exposed individuals have not yet been clarified.

We previously detected photoinitiators, including 1-hydroxycyclohexyl phenyl ketone (1-HCHPK), methyl 2-benzoylbenzoate (MBB), and 2-methyl-4′-(methylthio)-2-morpholino propiophenone (MTMP), in marketed injection solutions using gas chromatography-mass spectrometry (Kawasaki et al., 2012; Yamaji et al., 2012; Tsuboi et al., 2016). Injection solutions containing MTMP were administered to adults at a total dose of 1 L/day, and approximately 5.6 mg of MTMP per day accumulated in the body (Kawasaki et al., 2012). However, the pharmacokinetics of MTMP have yet to be elucidated in detail. We showed that MTMP induced apoptosis through a caspase-dependent pathway via caspase-3/7 *in vitro* (Kawasaki et al., 2013). Moreover, 1-HCHPK, MBB, and MTMP did not exhibit mutagenicity in the Ames test. However, UV-irradiated MTMP was associated with frameshift mutations in bacteria (Takai et al., 2018). Reitsma et al. (2013) previously reported that the photoinitiator 2-isopropylthioxanthone (2-ITX), which is used in ink, exhibited endocrine-disrupting activity *in vitro*. We also demonstrated that 1-HCHPK, MBB, and MTMP exhibited endocrine-disrupting activities and interacted with the estrogen receptor (ER) as agonists in the MCF-7 breast cancer cell line. Furthermore, a pretreatment with an ER antagonist blocked the proliferative capacity of each photoinitiator. Based on these findings, we suggested that photoinitiators have estrogenic properties (Morizane et al., 2015).

The development of breast cancer is associated with several factors, including estrogen exposure. Estrogen exerts physiological and pathophysiological effects by regulating the expression of target genes via ER alpha (ESR1), which functions as a transcription factor (Kelsey and Berkowitz, 1988). ESR1 as a receptor transcription factor plays an important role in the development of breast cancer, endometrial cancer, and ovarian cancer, in addition to the effects of female hor-

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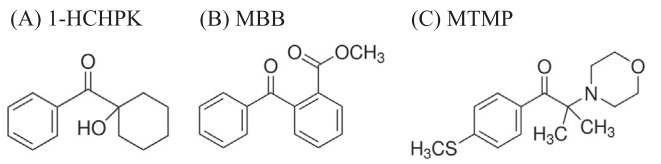

Fig. 1. Chemical structures. A: 1-Hydroxycyclohexyl phenyl ketone (1-HCHPK), B: methyl 2-benzoylbenzoate (MBB), and C: 2-methyl-4′-(methylthio)-2-morpholinopropiophenone (MTMP).

mones, such as normal mammary gland development (Persson, 2000). Therefore, estrogen is closely involved in the growth and progression of breast cancer, and ESR1 antagonists, such as tamoxifen (Tam) and aromatase inhibitors, have been clinically applied as endocrine therapy for breast cancer (Huang et al., 2000). Moreover, the treatment outcomes of breast cancer are affected by the expression of hormone receptors, such as ESR1 and human epidermal growth factor receptor 2 (HER2) (Barnard et al., 2015). Therefore, ESR1 antagonists and anti-HER2 antibodies are mainly used in endocrine therapy for breast cancer worldwide. Tam is commonly employed in clinical settings because it was the first selective estrogen receptor modulator to be developed (Mürdter et al., 2011). The long-term administration of Tam reduced the recurrence and mortality rates of breast cancer in the ATRAS study (Davies et al., 2013). Based on these findings and with the ultimate aim of preventing breast tumor progression, we investigated the endocrine-disrupting activities of photoinitiators *in vivo*. Therefore, the present study examined the estrogenic activities of 1-HCHPK, MBB, and MTMP using a mouse xenograft model with MCF-7 breast cancer cells.

Materials and methods

Drugs

MCF-7, an estrogen-sensitive human breast cancer cell line, was obtained from the RIKEN BioResource Center (Ibaraki, Japan). Dulbecco's modified Eagle medium (DMEM) and fetal bovine serum (FBS) were purchased from Life Technologies Japan Ltd. (Tokyo, Japan). Dimethyl sulfoxide (DMSO), 1-HCHPK, phosphate-buffered saline (PBS) (pH 7.4), and Tam (ER antagonist) were purchased from Sigma-Aldrich Co. (MO, USA). MBB and MTMP were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Matrigel® Matrix was purchased from Corning Japan K.K. (Osaka, Japan). In the *in vivo* study, all drugs were dissolved in DMSO and subcutaneously administered at a volume of 1 mL/kg. The chemical structures of the photoinitiators used in the present study are shown in Fig. 1.

Cell culture

The MCF-7 human breast cancer cell line was cultured in DMEM supplemented with 10% (v/v) heat-inactivated FBS, 100 units/mL of penicillin, and 100 μg/mL of streptomycin. Cells were maintained at 37 °C in an incubator with 5% (v/v) CO_2 in a water-saturated atmosphere.

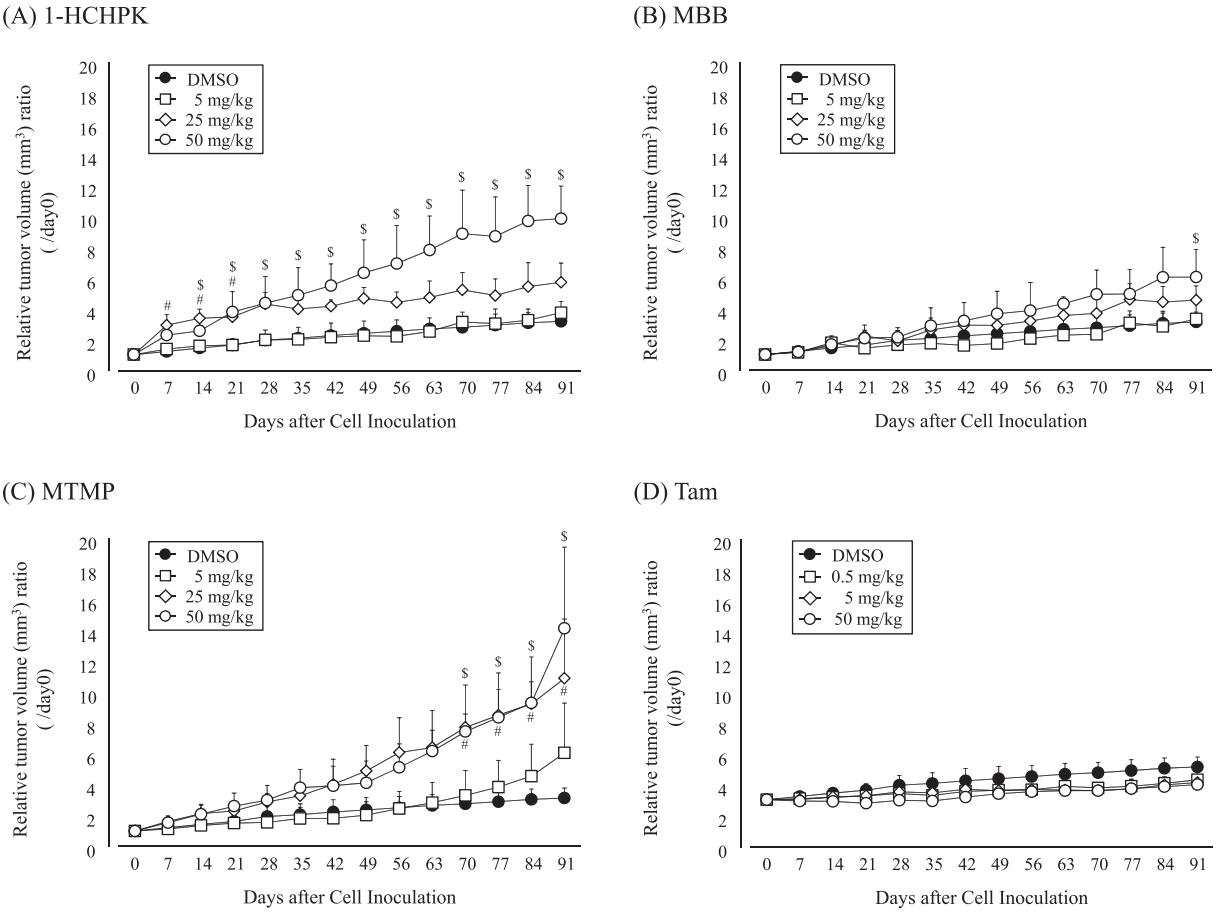

Fig. 2. Photoinitiator or tamoxifen treatments promoted breast tumor growth in an *in vivo* murine model. MCF-7-xenografted tumors were generated in BALB/c nude mice. (A) 1-HCHPK, (B) MBB, (C) MTMP, and (D) Tam. Results are presented as the mean ± SD (n = 5). $^{\#}p < 0.01$, $^{\$}p < 0.01$ significantly different from the control (DMSO-treated) group. # indicates a significant difference in the 25 mg/kg group. $ indicates a significant difference in the 50 mg/kg group.

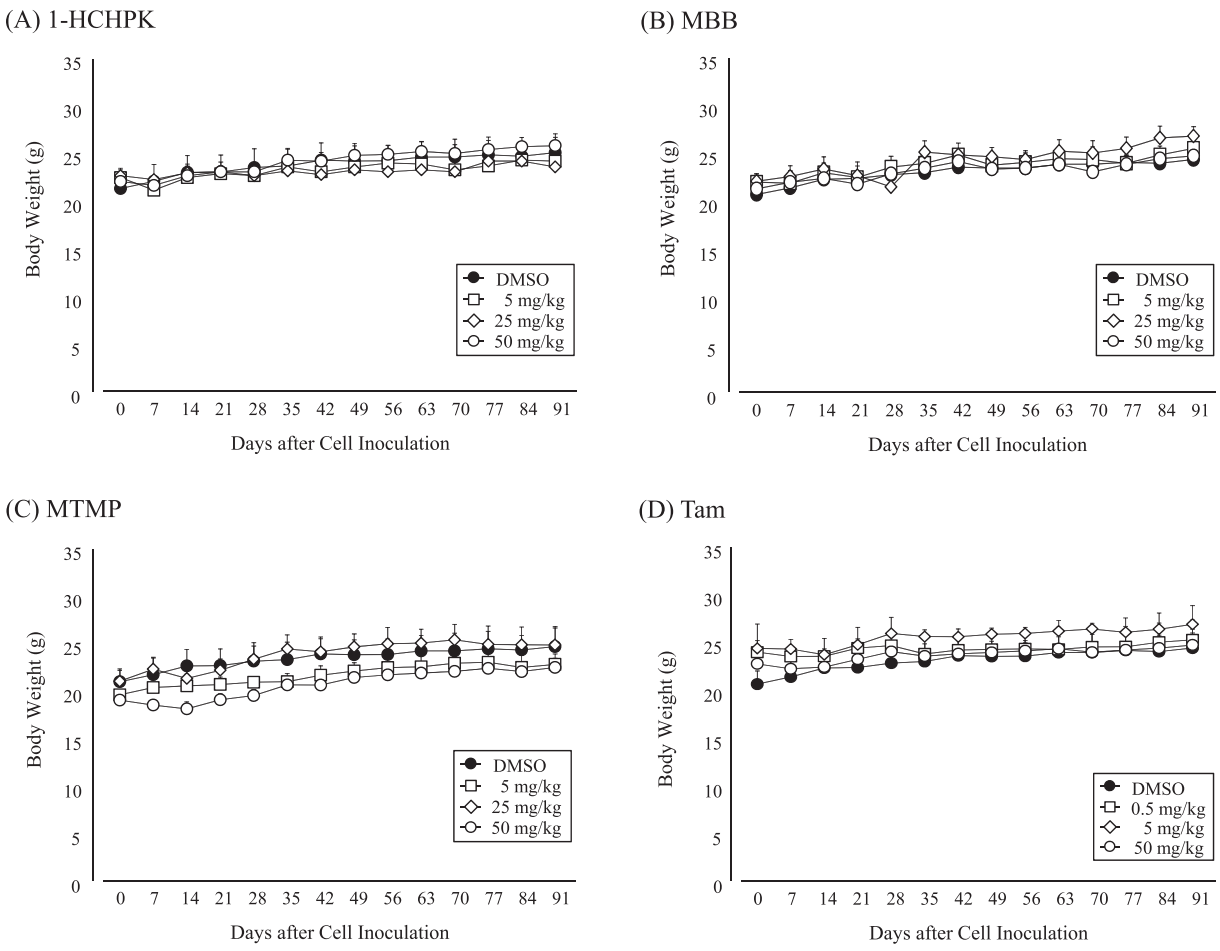

Fig. 3. Photoinitiator or tamoxifen did not affect body weight in an *in vivo* murine model. MCF-7-xenografted tumors were generated in BALB/c nude mice. (A) 1-HCHPK, (B) MBB, (C) MTMP, and (D) Tam. Results are presented as the mean ± SD (n = 5).

Subjects

Female BALB/c-nu mice (Charles River, Yokohama; initial weight 11–19 g) were housed four or five per cage under climate-controlled conditions with a room temperature of 23 ± 1 ˚C with a 12-h light–dark cycle (lights on at 8:00 a.m.). Food and water were available *ad libitum*. Experiments were performed in accordance with the Guidelines of the Ethics Review Committee for Animal Experimentation of Okayama University Medical School.

Tumor-xenografted model mice

The mouse xenograft model was established according to a previously described method (Faustino-Rocha et al., 2013). MCF-7 breast cancer cells (1×10^6) were suspended in PBS and mixed with Matrigel® Matrix at a ratio of 1:1 in 200 μL. Suspended cells were subcutaneously injected into 6-week-old female BALB/c-nu mice. When the estimated tumor volume was 100–300 mm^3, mice were randomly separated into five mice/treatment group and administered a photoinitiator (5–50 mg/kg), Tam (0.5–50 mg/kg), or a combination of Tam (0.5–50 mg/kg) + the photoinitiator (50 mg/kg) via a subcutaneous injection once a day for 2 weeks. Tam (0.5–50 mg/kg) was administered 30 min before the challenge with each photoinitiator (50 mg/kg). Body weights and estimated tumor volumes were measured each week using a scale and Vernier caliper, respectively. The estimated tumor volume was calculated using the formula V = (W (2) × L)/2, where V is the volume of the tumor, W is the width of the tumor, and L is the length of the tumor. The observation period was 91 days after the start of drug administration.

Statistical analysis

Data were analyzed using a one-way analysis of variance (ANOVA) followed by Dunnett's test. The significance level was set at $P < 0.01$.

Results

Effects of 1-HCHPK, MBB, and MTMP on tumor growth in tumor-xenografted mice

As shown in Fig. 2, the 1-HCHPK treatment markedly increased tumor volumes. No significant differences were observed between the 5 mg/kg group and control group. However, the 25 mg/kg group showed significant increases in tumor volumes on day 7, followed by slight increases after day 21. In the 50 mg/kg group, significant time-dependent increases were observed in tumor volumes from day 14 (Fig. 2A). MBB-treated tumors grew in a time-dependent manner and significantly increased after day 91 in the 50 mg/kg group. On the other hand, no significant differences were noted between the 5 and 25 mg/kg groups and the control group (Fig. 2B). The MTMP treatment also markedly increased tumor volumes. No significant differences were observed between the 5 mg/kg group and control group. Gradual increases in tumor volumes were noted in the 25 and 50 mg/

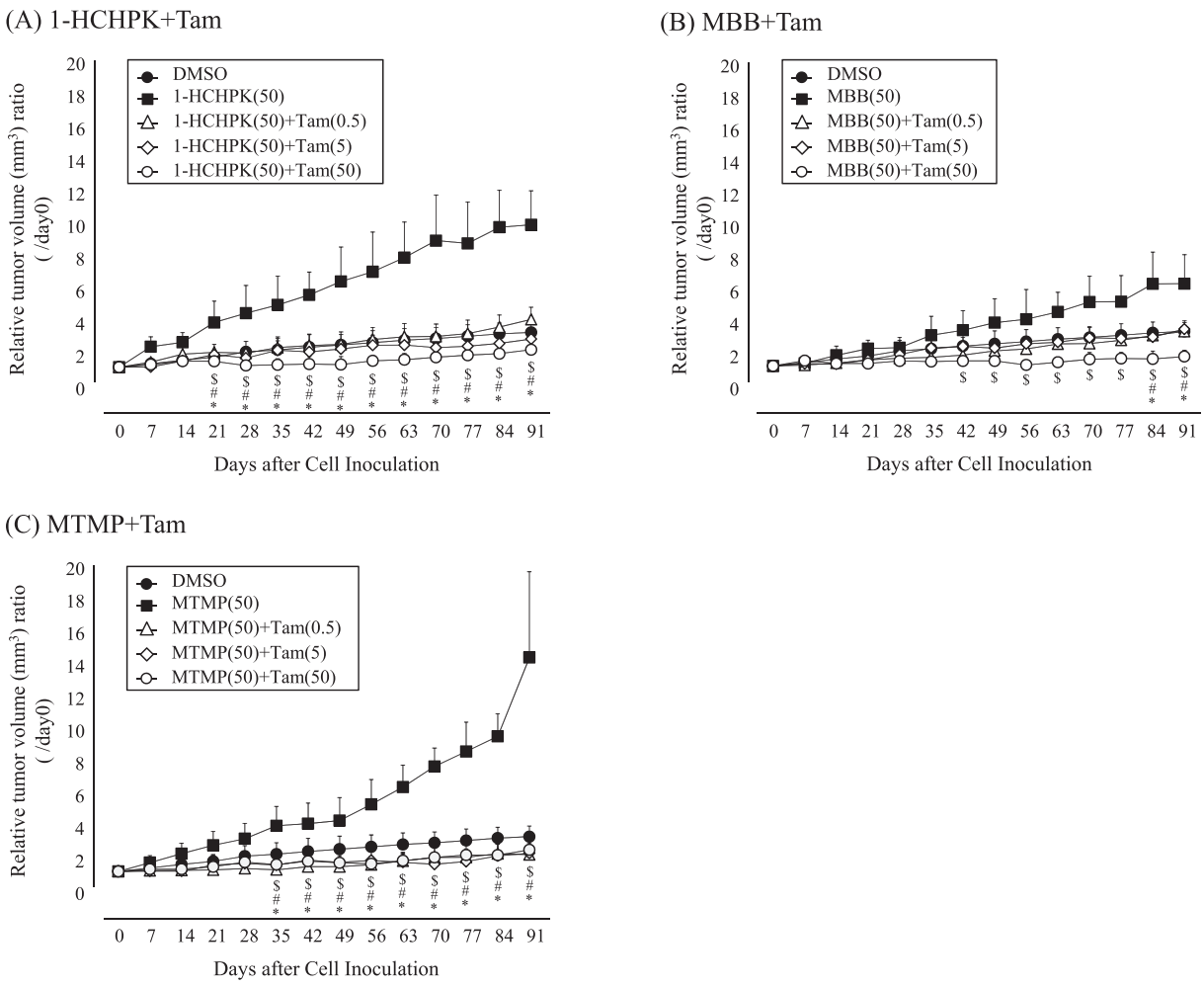

Fig. 4. Combination treatments suppressed breast tumor growth in an *in vivo* murine model. MCF-7-xenografted tumors were generated in BALB/c nude mice. (A) 1-HCHPK + Tam, (B) MBB + Tam, and (C) MTMP + Tam. Results are presented as the mean ± SD (n = 5). $^{*}p < 0.01$, $^{\#}p < 0.01$, $^{\$}p < 0.01$ significantly different from the control (DMSO treated) group. * indicates a significant difference in the photoinitiator (50) + Tam (0.5) group. # indicates a significant difference in the photoinitiator (50) + Tam (5) group. $ indicates a significant difference in the photoinitiator (50) + Tam (50) group.

kg groups, followed by significant increases after day 70 (Fig. 2C). However, body weight changes did not significantly differ among the groups (Fig. 3A, B and C).

Effects of Tam on tumor growth in tumor-xenografted mice

No significant differences were observed between the 0.5, 5 and 50 mg/kg group and control group. (Fig. 2D). Furthermore, body weight changes did not significantly differ among the groups (Fig. 3D).

Influence of the ER antagonist on effects of photoinitiators in tumor-xenografted mice

In 1-HCHPK-treated mice, the pretreatment with the ER antagonist Tam reversed 1-HCHPK-induced increases in tumor volumes (Fig. 4A). Tam (0.5, 5, and 50 mg/kg) significantly suppressed 1-HCHPK-induced increases from day 21.

In MBB-treated mice, the pretreatment with Tam reversed MBB-induced increases in tumor volumes (Fig. 4B). Tam at 0.5, 5, and 50 mg/kg significantly suppressed MBB-induced increases from days 84, 84, and 42, respectively

In MTMP-treated mice, the pretreatment with Tam reversed MTMP-induced increases in tumor volumes (Fig. 4C). Tam at 0.5, 5, and 50 mg/kg significantly suppressed MTMP-induced increases from day 35. However, body weight changes did not significantly differ among the groups (Fig. 5A, B and C).

Discussion

In the present study, we confirmed the estrogenic activities of photoinitiators *in vivo*. 1-HCHPK, MBB, and MTMP promoted tumor growth in a mouse xenograft model. In addition, a pretreatment with the ER antagonist Tam blocked the increases induced in tumor volumes by each photoinitiator after tumor formation. These results indicate that the three photoinitiators may exhibit estrogenic agonist activities *in vivo*. Furthermore, as factors for breast tumor growth, these photoinitiators may have estrogenic properties *in vivo*.

Tumor volumes were approximately 9.8-fold larger in 1-HCHPK-treated mice than in control mice with an observation period of 91 days. On day 91, tumor volumes were approximately 6.1-fold larger in MBB-treated mice than in control mice. Similarly, after day 91, tumor volumes were approximately 14.2-fold larger in MTMP-treated mice than in control mice. In our previous study using an MCF-7 breast cancer cell line *in vitro*, three photoinitiators (10^{-5} M) had approximately 2-fold higher proliferative effects than the control (Morizane et al., 2015). We attributed the differences between *in vitro* and *in vivo* findings to the chemical structures of the photoinitiators and the metabolic activities of the cell line and organs. Among

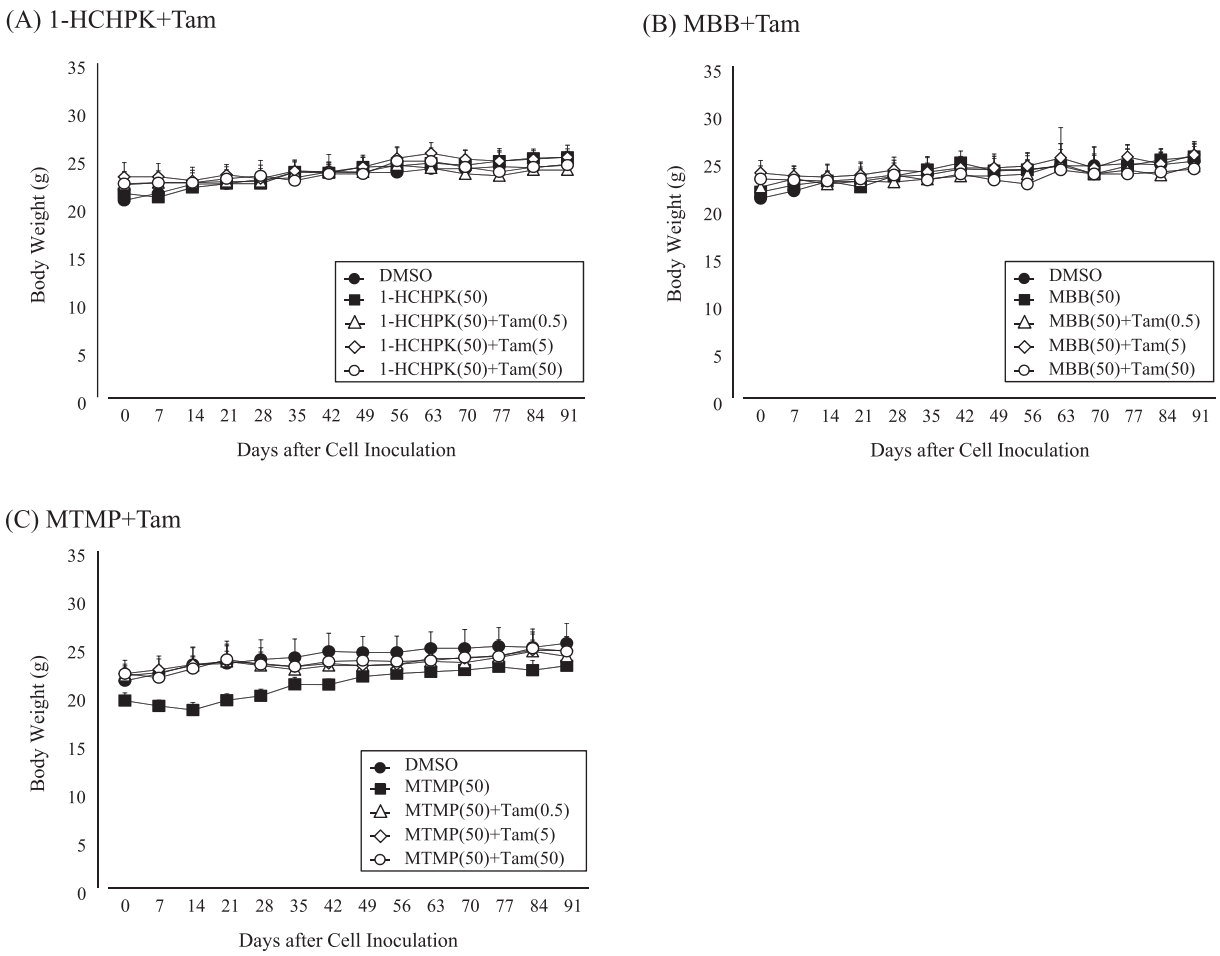

Fig. 5. Combination treatments did not affect body weight in an *in vivo* murine model. MCF-7-xenografted tumors were generated in BALB/c nude mice. (A) 1-HCHPK + Tam, (B) MBB + Tam, and (C) MTMP + Tam. Results are presented as the mean ± SD (n = 5).

the three photoinitiators examined, only MBB has an ester bond in its chemical structure. This ester bond was previously reported to be degraded by carboxyesterase in the body (Chen et al., 2016). Therefore, the increases induced in tumor volumes by MBB, which contains an ester bond, were considered to be smaller than those by 1-HCHPK and MTMP. Therefore, the tumor growth-promoting effects of the photoinitiators on breast tumors were due to *in vivo* factors.

In the present study, tumor volumes were significantly larger in 1-HCHPK-treated mice than in control mice on day 7; however, they were significantly larger in MBB- and MTMP-treated mice than in control mice on day 91 and day 70, respectively. These differences were attributed to the affinity of the photoinitiators for ER. Based on an X-ray crystal structure analysis of the 4-hydroxy Tam-ER complex, 4-hydroxy Tam may have stronger binding affinity than Tam due to the hydrogen bond between the hydroxyl group of the side chain of the benzene ring and the glutamic acid residue of the receptor (Wang et al., 2006). In addition, the binding affinity of FCE25071, an exemestane active metabolite (reduced to a hydroxyl group at position 17), was previously reported to be stronger than that of exemestane. The IC_{50} of exemestane is 545 nM, whereas that of FCE25071 is 6.1 nM (Ariazi et al., 2007). Among the three types of photoinitiators examined in the present study, only 1-HCHPK has a hydroxyl group. The hydroxyl group of the side chain of this photoinitiator may have influenced the extent to which tumor growth was promoted. On the other hand, gene mutations, which increase the possibility of developing breast cancer, are also risk factors (Sun et al., 2017). The regulation of ER expression in breast cancer was previously shown to involve ER gene methylation (Giacinti et al., 2006), ER gene mutations (Herynk and Fuqua, 2004), and the microRNA regulation of ER expression (Adams et al., 2007). Based on these findings, the affinity of photoinitiators for ER and their effects on the expression of proteins that regulate ER expression need to be investigated in future studies.

In *in vitro* studies on photoinitiator-induced endocrine disruption, D,L-camphorquinone exerted weak anti-androgenic effects (Shimamura et al., 2002). In addition, 2-ITX was found to potentially possess estrogenic and androgenic properties (Peijnenburg et al., 2010). 2-ITX was also shown to regulate androgen receptors and ER and modulate steroid biosynthesis (Reitsma et al., 2013). Based on these findings, we considered the three photoinitiators to also regulate hormone levels. Typical endocrine-disrupting chemicals (EDCs) exhibit estrogenic activity (Maqbool et al., 2016). ER is a ligand-dependent transcription factor in the nucleus of cells that mediates the effects of estrogen by binding to the estrogen response element (ERE) in the genome and directly controlling the expression levels of target genes in its vicinity. Estrogen-related receptor α (ERRα), a nuclear receptor with the highest homology to ER, binds ERE and regulates transcription (Stein and Yang, 1995; Paech et al., 1997). In addition, previous studies demonstrated that estrogen-bound ESR1 interacted with SP1, AP-1, and NFκB, bound to the promoter region of target genes, and was involved in the regulation of expression (Delfino and Walker, 1999; Kushner et al., 2000; Safe and Kim, 2004). Moreover, several EDCs are lipophilic and accumulate in body fat over time (Yilmaz et al., 2020). Since the three photoinitiators examined in the present study have similar chemical structures to

EDC in terms of lipophilicity, they were considered to be taken up by breast cancer cells. Therefore, photoinitiators may induce irreversible changes in the function or sensitivity of stimulatory/inhibitory signals. Further *in vitro* and *in vivo* studies are needed to establish whether photoinitiators play a role in the changes induced in the expression levels of major proteins and genes in breast cancer cells. Moreover, the mechanisms by which photoinitiators exert tumor growth-promoting effects need to be elucidated in more detail.

In conclusion, we herein demonstrated that three photoinitiators promoted the growth of breast tumors. The different tumor growth-promoting effects of these photoinitiators appeared to be due to differences in their chemical structures. Moreover, as a factor for breast tumor growth, photoinitiators may have estrogenic properties *in vivo*.

CRediT authorship contribution statement

Yoichi Kawasaki: Conceptualization, Methodology, Validation, Investigation, Funding acquisition, Formal analysis, Writing – original draft, Data curation, Project administration. **Toshiaki Sendo:** Methodology, Validation, Investigation, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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