What is new for an old Molecule? Systematic Review and Recommendations on the use of Resveratrol

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Supporting information:

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| **Table S1:** Effect of resveratrol on cancer development in experimental animals | | | | | |
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| **Species / Strain** | **Carcinogen** | **Resveratrol dose** | **Duration** | **Effect** | **References** |
| Skin - Non-melanoma skin cancer | | | | | |
| Female C3H/HeN mice | DMBA, 400 nmol, 1x / week | 10 µmol/ mouse prior carcinogen treatment | 25 weeks | Incidence: ↓ | [1] |
| SENCAR mice | DMBA |  | 4 weeks | Hyperplasia: ↓ | [2] |
| Female ICR mice | DMBA, 390 nmol/ mouse, 1.7 nmol TPA twice a week after 1 week and rest of exp. | 8.5 pmol Resv topically daily, 1 week prior initiation | 20 weeks | Multiplicity: ↓  Incidence: ↓ | [3] |
| Female CD-1 mice | Topically, 200 µmol of DMBA + 5 mmol of TPA | 1 – 25 µmol Resv, twice / week | 18 weeks | Incidence: ↓ all conc. used | [4] |
| CD-1 mice | Topically, 200 nmol DMBA + 5 nmol of TPA twice a week | 1 – 25 µmol Resv, twice / week | 18 weeks | Incidence: ↓ all conc. used | [5] |
| Female Swiss mice | Topically, DMBA (5 μg/animal) | 5 – 10 nmol Resv, 1 hour before DMBA | 28 weeks | Incidence: ↓ all conc. used | [6] |
| Skin – Melanoma | | | | | |
| Male Wistar rats | ip injection with AH-130 Yoshida ascites hepatoma cells | ip injection of 1 mg Resv/ kg bw/ day | 7 days | Growth of injected cell: ↓ | [7] |
| Male Nu/Nu-nuRB mice |  | 0.0025 or 0.006% Resv in diet (~ 3 or 7.2 mg Resv/ kg bw/ day) | 28 weeks | Latency: →  Incidence: → | [8] |
| Female C57BL/6N mice | B16-BL6 melanoma cells | 50 mg/ kg Resv ip injection daily | 9 days | Growth of injected cell: ↓ | [9] |
| Breast | | | | | |
| Female CD-1 mice | Top. appli. of DMBA | Pre incub. with 0.01 – 100 µM Resv twice / week | 18 weeks | Incidence: ↓ all conc. used | [4] |
| FVB/N female mice |  | 1 mg/l in drinking water, from week 20 (~ 0.1mg Resv/ kg bw/ day) | 10 weeks | Latency: ↓ | [10] |
| Female BALB/c mice | Injected mammary 4T1 mammary carcinoma cells | 1, 3 or 5 mg Resv/kg, ip daily | 23 days | Tumor volume: →  Lung metastases: → | [11] |
| Female Swiss mice | Ehrlich ascites carcinoma cells from a spontaneous mammary cancer | 20 or 40 mg Resv/kg, ip daily | 20 days | Tumor size:↓ (40 mg/kg) | [12] |
| Female Sprague-Dawley rats | Single i.v. dose of NMU, 50 mg/kg | 10 and 100 mg/ kg bw/ day ig, 5 days/week, starting 1 week prior MNU | 120 days | Latency: ↓, Multiplicity: ↓  Incidence: → | [13] |
| Female Sprague-Dawley CD rats | 60 mg DMBA /kg | Resv (1 g/kg diet) for full life span (~ 50 mg Resv/ kg bw/ day) | 18 weeks | Latency: ↓, Multiplicity: ↓  Incidence: → | [14] |
| Female Sprague-Dawley rats | Day 52 of age: 10 mg DMBA | Day 45 of age and the rest of study: 0.5 mg Resv / kg bw (in the diet) | 120 days after DMBA treatment | Multiplicity: ↓  Incidence: ↓ | [15] |
| Female Sprague–Dawley rats | Single i.v. dose of NMU, 50 mg/kg (on day 49) | sc inject. Resv (10 or  100 mg/ kg) for five days | 40 weeks | Incidence: ↑ | [16] |
| Liver cancer | | | | | |
| Balb/C mice | Injected mouse hepatocellular carcinoma  cells H22 | ip injected with Resv: 500, 1000 or 1500 mg/ kg | 10 days | Growth of H22 *in vivo:* ↓ , all conc. Used | [17] |
| Balb/c mice | Transplanted hepatoma cells | ip injected with Resv: 5, 10 or 15 mg/ kg | 10 days | Tumor size: ↓ , all conc. used | [18] |
| C57BL/6J mice | Intrasplenic injection B16 melanoma cells | Oral: 20 mg/kg 2 times/ day or 23 mg/L in drinking water | 10 days | Metastasis: ↓ | [19] |
| Sprague–Dawley rats | DENA, 200mg/kg, ip +  phenobarbital (0.05%) in  drinking water | Resv in diet equiv. to 50, 100 or 300 mg/kg bw /day, start 4 weeks prior initiat. | 4 + 20 weeks | Incidence: ↓ all conc. used  Multiplicity: ↓ all conc. used | [20] |
| Esophagus | | | | | |
| Male Sprague-Dawley rats | Esophagoduodenal anastomosis | ip injection with 7 mg Resv / kg | 5 months | Esophagitis: ↓  Incidence of intestinal metaplasia: →  Incidence of carcinoma: → | [21] |
| Gastric cancer | | | | | |
| Female Balb/C nude mice | sc injection of human primary gastric  cancer cells | 500, 1000 or 1500 mg/kg Resv, injected beside tumor, 6x over 2 days | 2 days | Tumor volume:↓ (all doses) | [22] |
| Male NMRI mice | sc implanted with the MAC16 tumor cells | After 10-12 days: 1 mg Resv/ kg ip injection daily | 3 days | Tumor volume:↓ | [23] |
| Colorectal cancer | | | | | |
| Male Wistar rats | 20 mg DMH /kg, once a week for 15 weeks | 8 mg Resv/ kg / day, either simultaneously with DMH, after DMH treatment or in the entire period | 15 / 30 weeks | ACF: entire treatm. Period: ↓  Adenoma / Adenocarcinoma: ↓  Incidence:↓, Multiplicity: ↓ | [24–26] |
| Male F344 rats | 15 mg AOM/ kg 2x 1 week apart | 10 days prior to carcinog. treatment: 200 µg / kg bw/ day in drinking water | 100 days | ACF incidence: ↓  ACF multiplicity: ↓ | [27] |
| CF-1 mice | ip injection of AOM (5 mg/kg body weight) | 20 mg/kg diet (~ 2.4 mg Resv/ kg bw/ day) | 5 weeks | Total ACF: ↓  ACF distal part: ↓  ACF multiplicity: → | [28] |
| Male C57BL/6J ApcMin/+ mice |  | 0.05% or 0.2% Resv in the diet (~ 60 and 240 mg Resv/ kg bw/ day). | 3 weeks | Adenomas: ↓ (0.2 % Resv) | [29] |
| Male C57BL/6J ApcMin/+ mice |  | 0.01% Resv in drinking water (~ 12 mg Resv/ kg) | 7 weeks | Small intestine adenomas: ↓  Colon adenomas: → | [30] |
| Male C57BL/6J ApcMin/+ mice |  | Dietary Resv correspond. to 0, 4, 20 and 90 mg/ kg bw/ day | 7 weeks | Tumor load: → | [31] |
| Male and female C57BL/6 mice | 10 mg AOM/kg bw  Water containing 1% DSS | 300 ppm Resv in diet (~ 48 mg/ kg bw/ day) | 62 days | Tumor incidence: ↓  Multiplicity: ↓ | [32] |
| Prostate | | | | | |
| Male Sprague–Dawley rats (SV-40 Tag) |  | 250 mg Resv/ kg in diet (~ 15 mg/ kg bw/ day) | 30 weeks | Incidence: ↓ | [33] |
| Male heterozygous TRAP rats |  | 50, 100 or 200 µg Resv/ ml in drinking water (~ 5, 10 or 20 mg/ kg bw/ day) | 7 weeks | Neoplastic lesions:↓ | [34] |
| Male PTEN-KO  mice |  | 50 mg / kg / by oral gavages, 3 times a week | 7 weeks | Adenoma incidence :↓ | [35] |
| Male athymic nude  BALB/cAnNCr-nu/nu mice | sc injection of LNCaP cells | 50 or 100 mg / kg diet, starting 2 weeks before inoculation of cells water (~ 6 or 12 mg/ kg bw/ day) | 9 weeks | tumor growth:↓ | [36] |
| Lung | | | | | |
| Female A/JOlaHsd mice | 80 or 300mg B[a]P /kg bw (gastric tube) once a week for 8 weeks | 0.4% Resv in diet  (~ 280 mg/ kg bw/ day) | 6 months | Incidence: →, Multiplicity: → | [37] |
| Female A/J mice | Weekly gavages doses of BaP + NNK (3 µmol of each) for eight weeks | 500 ppm in diet, starting 1  week after the final dose of BaP and NNK (~ 60 mg/ kg bw/ day) | 26 weeks, 18 weeks with Resv | Incidence: →, Multiplicity: → | [38] |
| Female C57BL/6N mice | B16-BL6 melanoma cells | 50 mg/ kg Resv ip injection daily | 9 days | Lung colonization: → | [9] |
| Female C57BL/6  mice | sc injection of Lewis lung carcinoma cells | Resv (0.6, 2.5 or 10 mg/ kg) ip once daily | 22 days | 2.5 or 10 mg/kg Resv:  Tumor weight: ↓  Tumor volume: ↓ | [39] |
| Neuroblastoma | | | | | |
| Male A/J mice | sc injection with neuro-2a cells | 40 mg Resv /kg / day | 28 days | Tumor volume: ↓ | [40] |
| Leukemia | | | | | |
| BALB/c mice | ip injection with L1210 cells | ig administration 12.5, 25, 50 mg/ kg /day | 3 weeks | Life span of tumor-bearing mice (dose-dependently): ↑ | [41] |
| ip: intraperitoneally; ig: intragastically; sc: subcutaneous; bw: body weight  AOM: Azoxymethane; B[a]P: Benzo[a]pyrene; DENA: Diethylnitrosamine; DMBA: 7,12-dimethylbenzanthracene; DMH: 1,2-dimethylhydrazine; DSS: dextran sulfate sodium; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; TPA: 12-0-tetradecanoylphorbol-13-acetate;  ACF: aberrant crypt foci;  Effect is indicated by ↓: reduction; ↑: enhancement; →: no effect. | | | | | |

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