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Veronica R. Bruce
University of New Mexico and Lovelace Respiratory Research Institute, Albuquerque, NM

Steven A. Belinsky
Lovelace Respiratory Research Institute, Albuquerque, NM

Katherine Gott
Lovelace Respiratory Research Institute, Albuquerque, NM

Yushi Liu
Lovelace Respiratory Research Institute, Albuquerque, NM

Thomas March
Consultant Veterinary Pathologist, Albuquerque, NM

See next page for additional authors

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Authors
Veronica R. Bruce, Steven A. Belinsky, Katherine Gott, Yushi Liu, Thomas March, Bobby Scott, and Julie Wilder

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Veronica R. Bruce □ University of New Mexico, Biomedical Sciences Graduate Program, Health Sciences Center, and Lovelace Respiratory Research Institute, Respiratory Immunology Program, Albuquerque, NM

Steven A. Belinsky □ Lovelace Respiratory Research Institute, Lung Cancer Program, Albuquerque, NM

Katherine Gott □ Lovelace Respiratory Research Institute, Respiratory Immunology Program, Albuquerque, NM

Yushi Liu □ Lovelace Respiratory Research Institute, Biostatistics, Albuquerque, NM

Thomas March □ Consultant Veterinary Pathologist, Albuquerque, NM

Bobby Scott □ Lovelace Respiratory Research Institute, Pathophysiology, Albuquerque, NM

Julie Wilder □ Lovelace Respiratory Research Institute, Respiratory Immunology Program, Albuquerque, NM

□ Low-dose ionizing radiation (LDR) may lead to suppression of smoking-related lung cancer. We examined the effects of a known cigarette smoke carcinogen Benzo[a]pyrene (B[a]P) alone or in combination with fractionated low-dose gamma radiation (60 – 600 mGy total dose) on the induction of lung neoplasms in the A/J mouse. Our results show that 600 mGy of gamma radiation delivered in six biweekly fractions of 100 mGy starting 1 month after B[a]P injection significantly inhibits the development of lung adenomas per animal induced by B[a]P. Our data also indicated that the six biweekly doses suppressed the occurrence of spontaneous hyperplastic foci in the lung, although this suppression failed to reach statistical significance when analyzed as average foci per lung possibly related to the small sample sizes used for the control and test groups.

KEY TERMS: Low-dose gamma-radiation, Benzo[a]pyrene, lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer mortality in both men and women in the United States and will soon reach epidemic proportion worldwide (American Cancer Society, 2012). Thus, lung cancer prevention is currently an active research area (Belinsky *et al.* 2003; Lyon *et al.* 2009). The most important risk factor for lung cancer is tobacco smoking

Address correspondence to Veronica R. Bruce, Lovelace Respiratory Research Institute, Respiratory Immunology Program, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108. Phone: 505-348-9562, Fax: 505-348-8567, Email: vgonzales@lrri.org

(Sanders and Scott 2008); it is estimated to account for up to 90% of lung cancer risk in men and up to 80% in women (Walser *et al.* 2008). Cigarette smoke contains approximately 5000 reactive chemical compounds and carcinogens that can lead to the development of lung cancer by damaging DNA and inducing inflammation through the recruitment of inflammatory cells (Yao and Rahman 2009). One of these compounds is Benzo[a]pyrene (B[a]P), a polycyclic aromatic hydrocarbon (PAH). Metabolites of B[a]P (e.g. benzo[a]pyrenediolexposide, BPDE) are mutagenic and carcinogenic. B[a]P causes DNA damage in lung cells consistent with DNA damage observed in malignant lung cancers (Denissenko *et al.* 1996), and its metabolites elicit a number of toxic effects in target cells such as DNA adduct formation, cytotoxicity of lymphocytes, and production of proinflammatory mediators such as certain cytokines (Wojdani *et al.* 1984; Umannova, *et al.* 2008). Studies conducted at our Institute have revealed an important role of epigenetic changes caused by BPDE exposure that are associated with neoplastic transformation of human lung epithelial cells and presumably also lung cancer development (Tellez *et al.* 2011).

The A/J mouse strain because of its known susceptibility to lung tumor induction by PAHs such as B[a]P, is commonly used to study lung cancer development after carcinogen exposure (Hecht *et al.* 1994; Malkinson 1992). In addition, the time course for development and progression of lung cancer (hyperplastic foci progressing to adenoma and finally carcinoma) can be easily quantified (Lyon *et al.* 2009*)*.

Although it is common knowledge that exposure to very high doses of radiation can induce cancer; a correlation between low doses of radiation and lung cancer has yet to be demonstrated. Recently scientists have shown that low-dose radiation can yield beneficial biological effects suggesting the potential of using low doses of radiation to combat cancer formation and reduce tumor prevalence and metastasis (Sakamoto *et al.* 1997). Researchers have investigated the effects of low-dose radiation, given as a single dose or fractionated or protracted over time, with regard to altering cancer development or resolution while others have focused on the effects of low-dose radiation on the systemic immune system (Liu 2003, 2007; Sakai *et al.* 2003; Sakai 2006; Thompson *et al.* 2008; Nowosielska 2010). The purpose of this study was to examine the effect of a known cigarette smoke carcinogen, alone or delivered in combination with low doses of low linear-energy-transfer (LET) gamma radiation, on the development of lung cancer in the A/J mouse. Our hypothesis is that low-dose gamma rays protect from B[a]P-induced lung cancer. In testing this hypothesis, we investigated the development of lung carcinogenesis 46 weeks after treatment of mice with B[a]P and the ability of fractionated gamma radiation (60 – 600 mGy total dose) to suppress cancer development.

MATERIALS AND METHODS

Animals:

Female, 10 week-old, A/J mice purchased from Jackson Laboratories (Bar Harbor, ME), were separated into the following groups: B[a]P only, B[a]P + radiation, radiation only, and age-matched unirradiated, untreated controls for a 46 week carcinogenesis experiment (n= 8-18 per group). At 46 weeks, mice were humanely euthanized by i.p. injection of a lethal dose of Euthasol.

Chemicals:

B[a]P (Sigma), at a concentration of 100 mg/kg body weight, was dissolved in 0.2 ml of tricaprylin (Glyceryltrioctanoate, Sigma) vehicle prior to interperitoneal (i.p.) injection.

Irradiation:

Mice were exposed to six biweekly whole body irradiations (WBI) at a dose rate of 1.07 mGy/s (10 mGy target dose) or 1.33 mGy/s (100 mGy target dose) from the Gammacell 1000 irradiator (^{137}Cs source) (Best Theratronics, Ontario, CA) for a total dose of 60 and 600 mGy, respectively. To achieve low doses, mice were exposed individually in polypropylene tubes set inside a stainless steel sample canister lined with lead foil (7.4 mm thickness). Experimental doses received were confirmed by nanoDots (Optically Stimulated Luminescence Technology, 1 cm^2, Landauer, Inc., Glenwood, IL) adhered to the outside of the tubes containing the mice. Initial dosimetry was performed using nanoDots inserted into the chests of mouse carcasses.

Histology

To estimate tumor burden, gross lung tumors were counted at necropsy. Lungs were inflated with neutral buffered formalin at a constant hydrostatic pressure of 25 cm for 6 hours and fixed further by immersion in formalin for >48 hours. Left lung lobes were systematically trimmed in a dorsoventral-transverse direction at 3-4 mm intervals with the first slice randomly positioned within the cranial 4 mm of tissue to yield 3-5 slices per lobe. A single slice along the axial airway of each of the right lung lobes was also made. Trimmed tissue was histoprocessed routinely, and 5 μm-thick paraffin sections were mounted and stained with hematoxylin and eosin for light-microscopic identification and enumeration of hyperplastic foci, adenomas, and carcinomas.

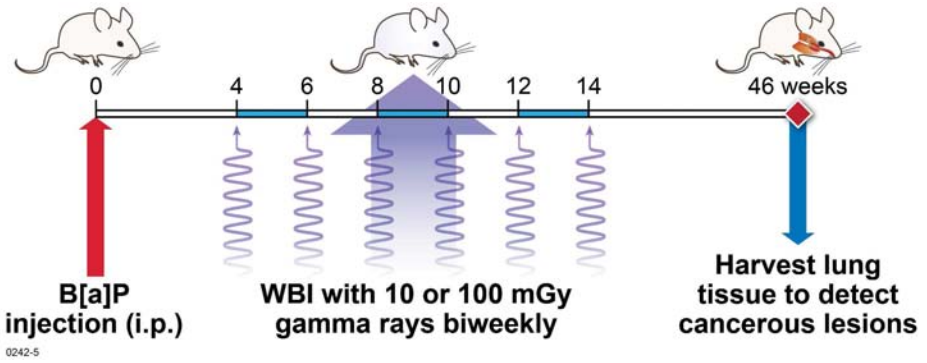

FIGURE 1. Study design. Mice were given a single dose of B[a]P four weeks prior to exposure to gamma radiation. Fractionated whole-body gamma-ray doses of 10 mGy or 100 mGy were then given once every 2 weeks until week 14 post-B[a]P injection for cumulative dose of 60 mGy and 600 mGy, respectively. At 46 weeks, lungs were harvested and lesions were enumerated grossly. In addition, lungs were fixed and tissue sections were prepared for histological examination.

Statistical Analyses

Tumor counts are given as means ± standard error (SE). Comparisons between groups were performed using the Wilcoxon Rank Sum Test except where otherwise stated.

RESULTS

Repeated 100 mGy gamma irradiation in B[a]P treated mice suppresses adenoma development

Various groups have previously demonstrated that animals exposed to single or fractionated low doses of X-rays or gamma-rays exhibit an attenuated growth of implanted cancerous tumors, and lung metastases are reduced when animals are exposed to radiation prior to inoculation with tumor cells (Hosoi and Sakamoto 1993; Cai 1999; Cheda *et al.* 2004; Nowosielska 2010). In order to ascertain whether low dose radiation could also inhibit lung carcinogenesis initiated by a PAH contained in cigarette smoke, we investigated the potential for suppression of cancer progression of B[a]P-induced lung tumors in mice exposed to repeated low doses of gamma radiation (Figure 1).

As expected, B[a]P treated mice exhibited a significantly higher number of lesions compared to control mice or mice receiving radiation only ($p < .05$, Figure 2A). The tumors observed grossly represented larger hyperplastic foci, adenomas, and carcinomas as well as non-proliferative lesions, such as inflammatory or fibrotic or non-lesions: multifocal pallor, atelectasis, and/or hyperinflation. These observations were proportional to those performed by histological analysis. In each B[a]P treated group, the number of hyperplastic foci greatly exceeded adenomas which in

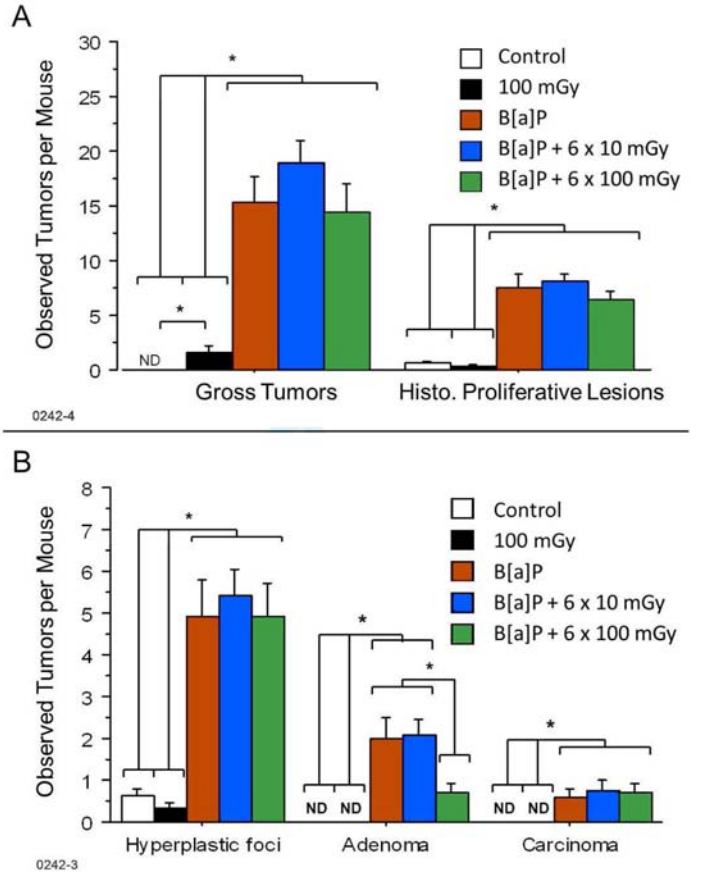

FIGURE 2. Lung tumors from mice injected i.p. with B[a]P four weeks prior to repeated irradiations with 10, and 100 mGy gamma-rays were grossly counted upon necropsy at 46 weeks post injection and histologically verified as proliferative lesions (A). Proliferative lesions (tumors) were further classified as hyperplastic foci, adenomas, or carcinomas (B). Mean values ± SE obtained from a single experiment is presented. Each experimental group contained 15-18 mice (n = 15-18), control group contained 8 mice (n = 8). Experimental groups are as described in materials and methods section. ND = not detected; * = $p < 0.05$ with the indicated groups being significantly different than each other on the same day of analysis.

turn exceeded carcinomas representing the natural progression of lung cancer (Figure 2B). In contrast, exposure of B[a]P treated mice to six fractions of 100 mGy doses of gamma radiation (600 mGy total) was associated with a significant reduction of adenomas compared to B[a]P alone (p = .04). Interestingly, as indicated in Table 1, a single histoproliferative lesion (hyperplastic focus) was found in 33 ± 11% of mice in the 600 mGy radiation group whereas 63 ± 17% of the age-matched, untreated control group had such a lesion (n = 8); however, further testing is needed to confirm this finding as the small group size of the age matched control mice did not allow for statistical significance to be achieved when evaluated on

TABLE 1. Tumor Incidence (% of mice with the indicated lesions) and standard error[a]

Group	No. Mice	% Mice with 1 or more Hyperplastic focus	% Mice with 1 or more Adenoma	% Mice with 1 or more Carcinoma
Control	8	62.5±17.1	0.0	0.0
100 mGy	18	33.3±11.1	0.0	0.0
B[a]P	12	91.7±8.0	75.0±12.5	41.7±14.2
B[a]P + 10 mGy	15	100.0	86.7±8.8	46.7±12.9
B[a]P + 100 mGy	14	92.9±6.9	57.1±13.2	50.0±13.4

[a]Standard error calculated assuming a binomial distribution of lesions

TABLE 2. *PROFAC*{*N*+} estimates for suppression of *N* or more B[a]P-induced adenomas via six bi-weekly 100-mGy, gamma-ray fractions to female A/J mice

"*N*"	*PROFAC*{*N*+}	Standard Error	Significantly > 0?
1	0.24	0.23	no
2	0.76	0.17	yes[b]
3	>0.79[a]	<0.23[a]	yes[b]

[a]Based on subjectively assigning 1 case among 14 animals when actually none had 3 or more adenomas per lung.

[b]Based on *PROFAC*{*N*+} minus 2 standard errors being > 0.

the basis of average foci per animal (p = .18). A more detailed analysis of these data (Scott *et al.* 2012) in the context of the hormetic relative risk (HRR) model (Scott *et al.* 2009; Scott 2011) demonstrated a significant gamma-ray protective effect against spontaneous hyerplastic foci. No adenomas or carcinomas were detected in the untreated control group or the group treated with six fractions of 100 mGy dose (Table 1).

We investigated the distribution of lung tumors (adenomas and carcinomas only) by exposure group. Our previously introduced HRR model incorporates a protection factor (*PROFAC*), which is the population average of individual-specific protection factors, *profac*, against lung tumor formation given that radiation has activated the body's natural anticancer mechanisms. The parameter *PROFAC* represents the on-average probability of lung tumor prevention when natural protection mechanisms have been activated in every individual (Scott *et al.* 2009; Scott 2011). With the HRR model, lung cancer relative risk (*RR*) is given by $RR = 1 - B(x)PROFAC$, where the benefit function $B(x)$ represents the probability that the body's natural defenses are activated by a low dose x of radiation.

To characterize the level of protection against B[a]P-induced lung tumors that is associated with *n* gamma-ray fractions, we introduce the *differential protection factor*, *PROFAC*{*N*+}, for protecting from cases of *N* or more lung tumors. Thus, *PROFAC*{1+} applies to protection from 1 or more lung tumors. *PROFAC*{2+} applies to protecting from 2 or more lung

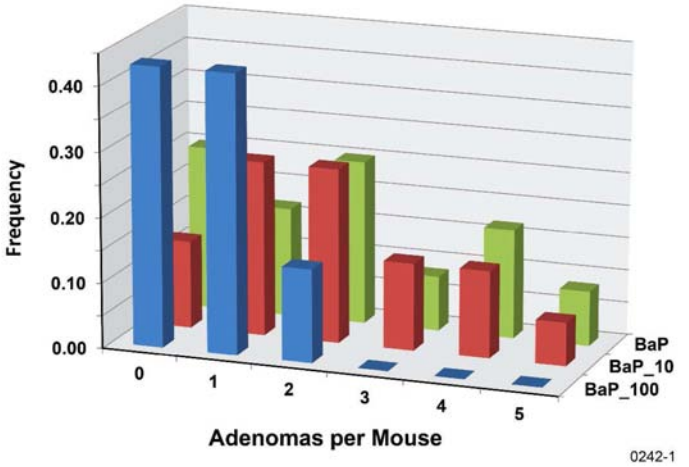

FIGURE 3. Frequency distribution of adenomas per mouse for the B[a]P-exposure-only group (BaP), for the group exposed to B[a]P and 10-mGy gamma-ray fractions (BaP_10), and for the group exposed to B[a]P and 100-mGy gamma-ray fractions (BaP_100).

tumors, etc. Table 2 shows results obtained for *PROFAC*{1+}, *PROFAC*{2+}, and *PROFAC*{3+} for protection from B[a]P-induced lung adenomas by six fractions of 100 mGy gamma-rays. In each case $B(x)$ was assumed to be 1 (e.g., protective mechanisms activated in each animal). Where values of *PROFAC*{*N*+} minus two standard errors was > 0, the *PROFAC* value reported was considered significantly > 0 (interpreted to indicate a significant protective effect). Thus, only protection against 2 or more and against 3 or more adenomas per animal were considered significant ($p < .05$). There was no indication of a gamma-ray protective effect by the six fractions of 10 mGy dose from adenomas or carcinomas (Figures 3 and 4).

DISCUSSION

As expected, B[a]P and/or specific metabolites (e.g., BPDE) induced lung cancer in this study detected as hyperplastic lesions, adenomas, and carcinomas. In contrast, mice exposed to radiation alone and unexposed control mice developed no adenomas or carcinomas that would indicate a progression to a more malignant phenotype. Treatment with six fractions of 10 mGy gamma irradiation did not result in a reduction of B[a]P-induced hyperplastic foci, adenomas, or carcinomas. The six fractions of 10 mGy gamma rays also did not alter the distribution of the tumors per mouse from what was found for the B[a]P-only exposure. However, repetitive exposure to six fractions of 100 mGy gamma radiation reduced the number of adenomas in B[a]P treated mice. Seventy-five ± 13% of B[a]P treated mice developed one or more adenomas compared to 57.1 ± 13%

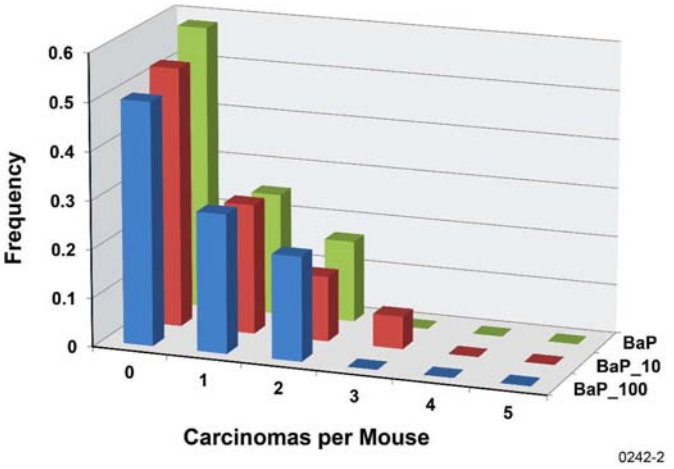

FIGURE 4. Frequency distribution of carcinomas per mouse for the B[a]P-exposure-only group (BaP), for the group exposed to B[a]P and 10-mGy gamma-ray fractions (BaP_10), and for the group exposed to B[a]P and 100-mGy gamma-ray fractions (BaP_100).

when six fractions of 100 mGy gamma rays were administered (fractionated) in addition to B[a]P (Table 1).

When investigating the distribution of B[a]P-induced lung adenomas we found a clear beneficial effect of the six fractions of 100 mGy gamma-ray exposure related to reducing the multiplicity of these lesions (3 or more) in the mouse lung. The lack of a gamma-ray protective effect against carcinomas may relate to the 46 week follow-up time used in the study design. We cannot rule out the possible occurrence of a protective effect against carcinomas for much longer follow-up times.

As a result of low-dose, gamma-ray exposure, spontaneous hyperplastic foci prevalence was reduced from non-irradiated controls from 0.63 to 0.33 (Figure 2B, Table 1), although not statistically significant due to the small sample sizes used. This finding is currently under further investigation. Interestingly, a reduction in spontaneous adenoma formation (*PROFAC*{1+}= 0.209 to 0.321) was observed in RFMf/Un mice when subjected to single whole-body doses of gamma radiation ranging from 100 up to 1500 mGy (Ullrich and Storer 1979). In humans, long-term residential radon exposure has been associated with a reduction rather than an increase in sporadic lung cancers for a range of average radon levels (Cohen 1997, Thompson *et al.* 2008, Scott 2011). A *PROFAC*{1+} > 0.5 has been implicated for the population studied by Thompson et al. in their 2008 paper (Scott 2011). Previously, protective effects of protracted, low-dose, low-LET gamma radiation has also been shown against high-LET, alpha-radiation-induced lung cancer in rats (Scott *et al.* 2008). A gamma-ray *PROFAC*{1+} close to 1 was reported for preventing lung tumor cases

in rats exposed to low doses (< 200 mGy) of highly-damaging alpha radiation where not more than 1 alpha-radiation-induced lung tumor per animal or not more than 1 spontaneous lung tumor per animal was expected (Scott *et al.* 2008; Sanders 2012). In contrast, low-dose gamma rays did not protect (*PROFAC*{1+} = 0) from lung tumor induction (one or more per animal) by very high doses (> 5000 mGy) of alpha radiation where multiple tumors per animal may have occurred among long-term survivors because of immune system suppression (Scott *et al.* 2009). The data were not analyzed to see if low dose gamma rays protected from multiple tumors per animal. Gamma-ray protection (*PROFAC*{1+} > 0.8) against alpha-radiation-induced (from inhaled plutonium-239) and smoking-related lung tumors has also been reported for humans (Scott 2007; Scott *et al.* 2009). The indicated data relate to chronic exposure of the lung at low rates over many years to both alpha and gamma radiations.

B[a]P primarily targets the lung when administered i.p., however we also observed lesions not of pulmonary origin. Seven out of 77 total mice were found to have lesions (hyperplasias, adenomas, carcinomas, or in combination) in tissues of the stomach, pancreas, and ovaries. These observations are consistent with those previously documented in which B[a]P induced injection site tumors and tumors in the abdomen and pancreas of mice injected i.p. (Hecht *et al.* 1994, Balansky *et al.* 2006). As there were so few mice observed to have these lesions, no analysis was performed to examine the effect of radiation.

In conclusion, results from this study suggests that six fractions of 100 mGy but not 10 mGy gamma radiation significantly reduces the multiplicity of adenomas but not carcinomas induced by B[a]P. Although not statistically significant, radiation also appears to decrease the number of cases of spontaneous hyperplastic foci by a similar degree as was reported by other researchers for gamma-ray prevention of cases of spontaneous lung cancer in mice (Ullrich and Storer, 1979). The mechanisms behind this phenomenon have yet to be fully elucidated, although there is growing evidence for a hierarchy of protective mechanisms being involved (Scott *et al.* 2009). Taken together, these findings support the hypothesis that low-LET radiation (e.g., gamma rays) given at low doses and dose rates can prevent lung cancer induction by agents such as cigarette smoke carcinogens.

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