Osteopontin (SPP1) expression has been identified in human lung cancer and has been linked with enhanced tumor progression. To examine its functional role, we induced lung tumors by repetitive urethane or MCA/BHT lung carcinogens in C57BL/6 mice lacking both (*Spp1-/-*), one (*Spp1+/-*), or no (*Spp1+/+*) copy of the endogenous *Spp1* gene. Primary end-points were lung tumor number and size; secondary end-points were SPP1 expression, epithelial cell survival, carcinogen-induced inflammation, and angiogenesis. Data are presented as mean±SD. Compared with *Spp1+/+* mice (n=22), *Spp1-/-* mice (n=25) developed dramatically fewer and significantly smaller lung tumors in response to urethane, while *Spp1+/-* mice (n=12) behaved similar to *Spp1-/-* mice (number/diameter of lung tumors in *Spp1+/+*, *Spp1+/-*, and *Spp1-/-* mice, respectively: 16.1±12.7/1.2±0.3 mm, 2.4±2.3/0.9±0.2 mm, and 1.3±1.6/0.7±0.2 mm; $P<0.05$ for comparison of *Spp1+/+* with *Spp1-/-* and *Spp1+/-* mice). *Spp1-/-* mice were also protected from two-hit MCA/BHT-oncogenesis compared with *Spp1+/+* controls. *Spp1-/-* mice displayed decreased epithelial cell survival and reduced numbers of airspace macrophages early after urethane, and enhanced tumor cell apoptosis and limited tumor angiogenesis at late stages of lung tumor progression. SPP1 was expressed in the naïve lung by non-ciliated airway epithelial cells and alveolar macrophages and was significantly up-regulated during multi-stage lung carcinogenesis. SPP1 also initiated the survival of mutant Kras cells. Our data indicate that SPP1 is functionally involved in airway epithelial carcinogenesis via survival of mutant Kras cells and may present a target for lung cancer treatment and prevention.