

n-6 Polyunsaturated Fatty Acids Increase Skin but not Cervical Cancer in Human Papillomavirus 16 Transgenic Mice¹

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ABSTRACT

Using a mouse with transgenes for the highly oncogenic human papillomavirus type 16, we asked whether a diet high in fat, namely, the *n*-6 polyunsaturated fatty acid linoleic acid, would influence the development of skin or cervical cancer. Virgin female keratin 14-human papillomavirus 16 transgenic mice were fed control diet or diet with 20% corn oil. The effect of these diets was compared in mice implanted or not implanted with 0.125 mg/60 day release of estradiol. More precancers and cancers of the skin developed faster in mice fed the high-fat diet. Estrogen had no effect on the development of skin cancers. In contrast, estrogen was necessary for the development of cervical cancer, and a high-fat diet had no effect on the development of cervical cancer.

INTRODUCTION

Dietary fat ranks as a risk factor for some prevalent cancers (1–8). Saturated fat is worse than unsaturated fat, and *n*-6 PUFAs³ increase cancer risk, whereas *n*-3 PUFAs decrease risk. Because high-fat diets increase the conversion of androgens to estrogen, it is not surprising that high-fat diets appear to increase the estrogen-enhanced breast and endometrium cancers. Even NMSC, the most common cancer among Caucasians in the United States, with an estimated one-half million new cases a year (9), appears to be affected by a high-fat diet (10–12). A low-fat diet (<20% of calories from fat) reduced the incidence of precancerous skin lesions and skin cancers in human patients with a history of NMSC (13). In animal studies, a high-fat diet increases the likelihood of skin tumors after exposure to UV radiation, and changing to a low-fat diet after the UV exposure reduces the incidence of skin cancer (14, 15). A high-fat diet also counteracted the inhibitory effect of an energy-restricted diet in a mouse model for chemically induced skin cancer (16). However, whereas PUFAs, including *n*-6 fatty acids, increase skin cancer in the mouse induced by UV radiation, PUFAs decrease skin cancers in certain chemically induced skin cancer models (17–19).

Certain HPV types render cells susceptible to cancers because they inactivate some tumor suppressors such as p53 and retinoblastoma (20, 21). Most notably, HPV is a cofactor for cervical cancer (22), and estrogen apparently promotes the development of this cancer (23, 24). Epidermodysplasia verruciformis is a HPV-associated skin disease resulting in NMSCs on sun-exposed areas of skin (25, 26). Although controversial, evidence is accumulating that some newly discovered HPV types may be cofactors for most NMSC (27–30). Prevailing data indicate that HPV infections occur early, are ubiquitous, and become latent and that prolonged UV irradiation is needed to activate viral gene functions. Consistent with the data from human studies on epidermodysplasia verruciformis, UV activates latent cottontail rabbit

papillomavirus (31), a papillomavirus that causes skin cancer in rabbits.

The possibility exists that a high-fat diet may influence the outcome of HPV-related cancers. As described above, fat appears to influence NMSC. Fat clearly influences estrogen levels, a factor for the development of cervical cancer. A mouse with transgenes for the highly oncogenic HPV16 exists that develops NMSC spontaneously (32). This mouse develops cervical cancer when given estrogen chronically (24). Vegetable oils contain the *n*-6 PUFA (linoleic acid), and *n*-6 PUFAs are known to promote the development and progression of mammary cancer in mouse models (33, 34) but have differential effects for skin cancers, depending on the promoter (14–15, 17–19). Because vegetable oils are the major fatty acid contributor in the Western diet, and growing evidence supports a HPV component in many NMSCs, we asked whether a diet rich in corn oil, which is almost exclusively linoleic acid, would influence the outcome of NMSC and/or cervical cancer in the mouse with HPV transgenes.

MATERIALS AND METHODS

Animals. The K14-HPV16 transgenic mice developed by Arbeit *et al.* (32) were described previously. The transgenes consist of the early region of the HPV16 genome controlled by the K14 promoter. Heterozygous virgin female mice (4–5 weeks old) were used in this study, and only littermates were housed together. Euthanasia was performed by CO₂ asphyxiation. The study was approved by the Institutional Care and Use Committee of the Long Island Jewish Medical Center.

Diet Studies. Control diet was AIN76a (5% corn oil with 22% of calories from protein, 11% of calories from fat, and 67% of calories from carbohydrate). The high-fat diet was AIN76 (20% corn oil with 19% of calories from protein, 37% of calories from fat, and 44% of calories from carbohydrate). Diets were purchased from Ziegler Brothers Inc. (Gardner, PA) and stored under nitrogen until used. Mice were implanted s.c. with 0.125 mg/60-day release pellets of 17 β -estradiol or placebo. Implants were repeated every 60 days until the end of the study. Mice were fed *ad libitum*.

Tissue Procurement and Histology. After euthanasia, ear skin was removed and fixed immediately in 10% formalin in PBS overnight. Similarly, the vagina, cervix, and both uterine horns were removed and fixed. Tissues were dehydrated through graded alcohol and xylene and embedded in paraffin. Five- μ m serial sections through the full tissue were prepared, mounted, deparaffinized, and stained with H&E.

Statistics. The χ^2 test was used for data analysis.

RESULTS

Phenotypic Effects of High-fat Diets. The K14-HPV16 transgenic mouse exhibits thickened ears and a scruffy coat of fur and becomes more mangy with age compared with the nontransgenic littermates (Fig. 1, A and B). As described previously (32, 35), warty lesions will occur in a subset of these mice, and some of these lesions become cancers in mice on control diets. The incidence of these lesions increases with age. In our studies with female mice, 1 of 16 mice on control diet (no estrogen implants) developed skin lesions by 7 months of age, whereas most of the remaining mice studied in the same group (12 additional mice) eventually developed skin lesions at a later age. Lesions usually occurred on or behind the ear and

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³ The abbreviations used are: PUFA, polyunsaturated fatty acid; HPV, human papillomavirus; NMSC, non-melanoma skin cancer; K14, keratin 14; PG, prostaglandin.

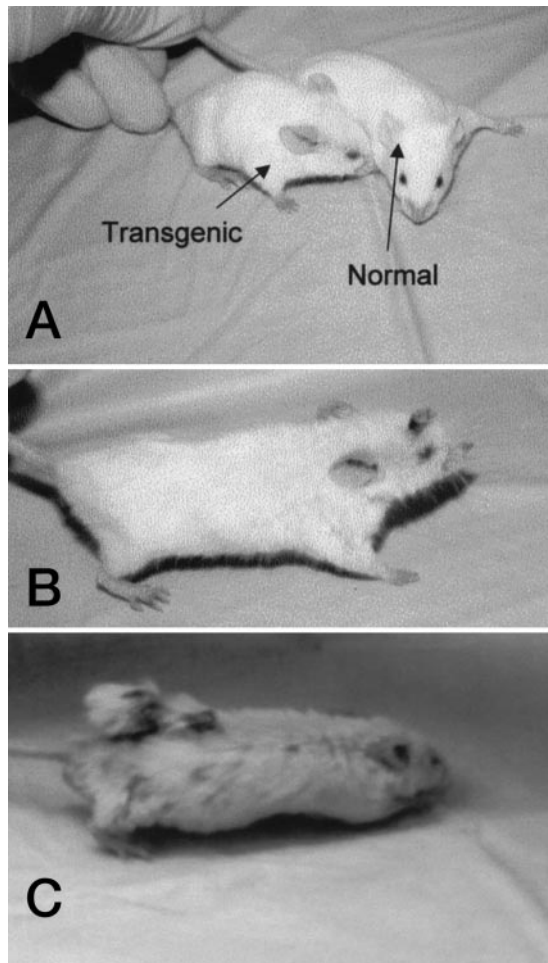


Fig. 1. Phenotypic appearance of K14-HPV16 mice. *A*, transgenic mouse (with thickened, reddish ears) and nontransgenic littermate; *B*, older transgenic mouse with solitary warty lesion on head; *C*, transgenic mouse fed diet supplemented with 20% corn oil with multiple small and large warty lesions.

sometimes occurred on the face or head, sites that are typically irritated by scratching (Fig. 1*B*). Male mice housed with other males, including littermates, develop more lesions at sites of injury caused by biting and fighting (data not shown).

Mice fed the high-fat diet developed much more skin pathology that could be detected visually (Fig. 1*C*). All mice on the high-fat diet, with or without estradiol, experienced hair loss under the chin and chest as early as 3 months after starting the diet. Lesions started to occur as early as 3–4 months and were usually multiple. The most severe lesions, *i.e.*, those more likely to become cancers, were typically on the ear. This contrasts with the typical appearance of lesions in mice fed control diet (see the description above). Mice on control diets developed tumors that were usually solitary and not observed until 6 months of age, usually older. No skin pathology was evident in the nontransgenic littermates, although these mice became obese on the high-fat diet (results not shown).

Effects of High-fat Diets on Skin Cancer. Mice with HPV transgenes have hyperplastic skin regardless of diet (Fig. 2*A*), and this is the cause of the thickened ears. By 7 months of age, most skin lesions turned out to be benign and exhibited dysplasia of varying severity (Fig. 2*B*). Similar to our previous studies (35), most cancers occurred in the skin of the ear in these studies. An example is shown in Fig. 2*C*. Studies compared the percentage of mice that developed cancers in ear epithelia. Mice were euthanized at 7 months, except for a subset of mice ($n = 12$) within the group fed the control diet and not treated

with estradiol. This subset was sacrificed at 12 months of age. When groups of mice on the high-fat diets were compared (Fig. 3), 33% ($n = 25$) and 26% ($n = 23$) of mice untreated or treated with estradiol developed skin cancer in one or both ears; <6% of mice in either of the groups on control diets developed skin cancer in one or both ears, regardless of whether or not they were treated with estradiol.

Effects of High-fat Diet on Cervical Cancer. Treatment with estradiol in both normal and transgenic mice results in hyperplasia and dysplasia of the cervical epithelium (24, 35). However, only transgenic mice treated with estradiol develop cervical cancer (24, 35). In this study (Fig. 4), no mouse (0 of 53 mice) developed cervical cancer in the combined diet groups that had no estradiol treatment. However, 68% of mice fed the control diet and 60% of mice fed the high-fat diet developed cervical cancer in the estradiol-treated groups (48 mice/group). An example is shown in Fig. 2*D*.

DISCUSSION

In this study, a diet made high fat with corn oil (almost exclusively the $n-6$ PUFA linoleic acid) increased the number of precancerous skin lesions and progression to skin cancer in mice with HPV transgenes driven by the K14 promoter. In contrast, cervical cancer was not increased. Additionally, this study supports the findings of other studies showing that estrogen is a cofactor for cervical cancer (24, 35, 36) and shows that estrogen is not a cofactor for skin cancer. Importantly, this study indicates that the $n-6$ PUFAs can be a cofactor for skin cancer, and the specific promoter for HPV-initiated cancer depends on the tissue site.

$n-6$ PUFAs could promote tumorigenesis by several mechanisms. High-fat diets increase estradiol by increasing aromatase and conversion of androgens to estrogen. We can eliminate increased estrogen as a possible mechanism because $n-6$ PUFAs did not increase the incidence of cervical cancer, and cervical cancer is dependent on estrogen in this model. Conversely, estrogen did not increase the incidence of skin cancer. A second possible mechanism involves inflammation. Linoleic acid is converted to arachidonic acid, which is converted to PGs by cyclooxygenases. PGs increase cell proliferation, promote angiogenesis, and inhibit immune surveillance, all of which favor the growth of malignant cells (reviewed in Refs. 37 and 38). Consistent with the possibility that PGs may contribute to skin cancer, both a specific inhibitor of cyclooxygenase-2 and indomethacine, an inhibitor of cyclooxygenases, have been shown to inhibit UV-induced skin cancer (39). Furthermore, immunosuppression in humans increases HPV skin lesions and subsequent cancers (40, 41), and much information indicating that PUFAs affect eicosanoid metabolism and immunosuppression exists. As another possibility, recent studies have demonstrated that PUFAs may influence the activity of the epidermal growth factor receptor/mitogen-activated protein kinase pathway, which could activate a number of oncogenes (reviewed in Ref. 42).

As described in the "Introduction," the issue of whether HPVs constitute a major risk for NMSCs is controversial. However, HPV16, the source of transgenes in this study, has been shown to be a factor in cases of Bowen's disease (43, 44), and HPVs inactivate certain tumor suppressors common to many cancers, rendering cells more vulnerable to malignant transformation. Regardless, the mouse model used in this study is yet another indication (not to mention human studies) that implicates that a high-fat diet promotes skin cancer. Clearly, the development of either cervical or skin cancer requires the HPV oncogenes in our mouse model because neither cancer occurs in the nontransgenic littermates fed the high-fat diet⁴ or given estrogen.

The fact that corn oil is a cofactor for this skin cancer, whereas

⁴ Unpublished results.

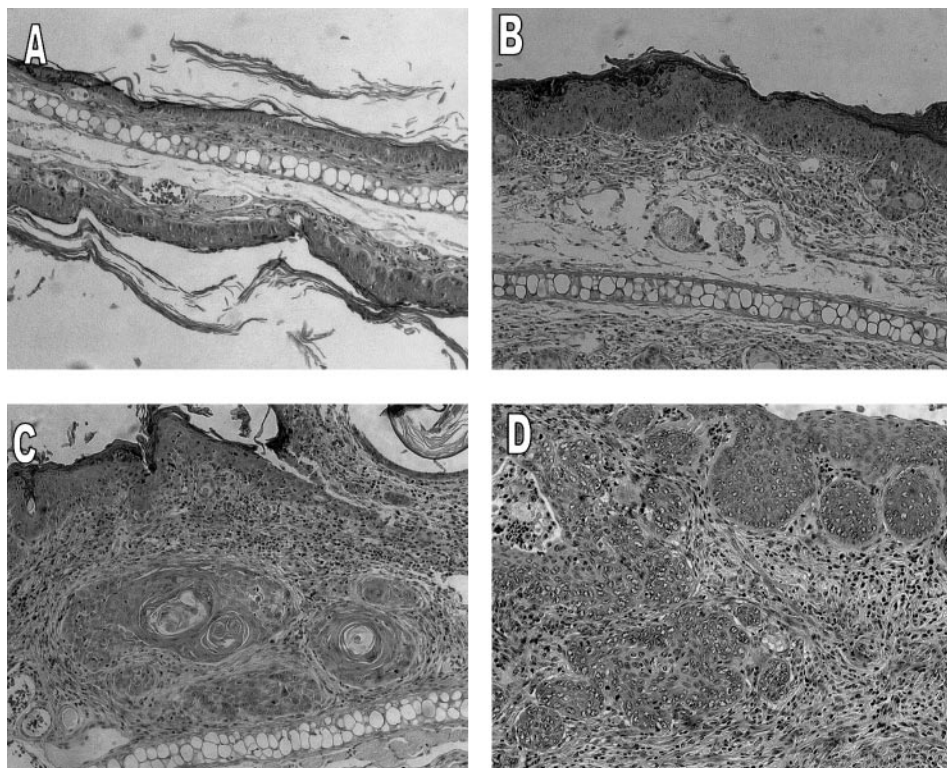


Fig. 2. Skin (ear) and cervical-vaginal sections of K14-HPV 16 mice. H&E staining shows (A) hyperplasia of ear epithelium, (B) dysplasia of ear epithelium, (C) invasive cancer of ear epithelium, and (D) invasive cancer of the cervix.

estrogen is a cofactor for cervical cancer, is intriguing. Different types of HPVs have tissue specificity, which is dependent, at least in part, on the regulatory regions within the viral genomes (45). However, the HPV transgenes are driven by the K14 promoter in this mouse model (24). Therefore, cellular factors, rather than viral factors, must be responsible for the differences observed. It appears that the *n*-6 PUFAs affect breast and cervical cancer cells differently. These data and our *in vitro* data (46) indicate that linoleic acid does not affect cervical cells transformed by HPV16. However, linoleic acid in-

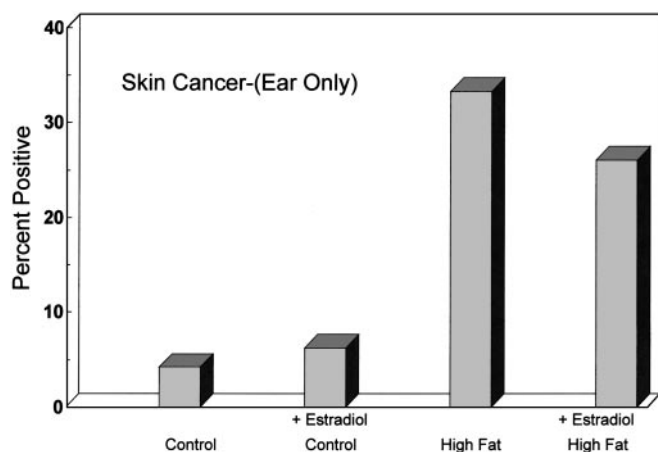


Fig. 3. *n*-6 PUFAs, but not estrogen, increase skin cancer in K14-HPV 16 mice. Ear epithelia (both ears) were harvested from mice after euthanasia and examined histologically. The time point was 7 months of age, except for a subset (euthanized at 12 months) within the group of untreated mice fed the control diet. The percentage of mice with invasive cancer in at least one ear was compared in mice fed control diet ($n = 28$), mice fed control diet and given slow-release estradiol ($n = 25$), mice fed high-fat diet ($n = 25$), and mice fed high-fat diet and given slow-release estradiol ($n = 23$). Comparing the amounts of skin cancer, $P = 0.047$ in mice fed control diet compared with mice fed the high-fat diet that were not treated with estrogen or $P = 0.035$ in mice fed control diet compared with mice fed the high-fat diet and treated with estrogen. There was no significant difference comparing estrogen treatment in the control groups or groups fed the high-fat diet.

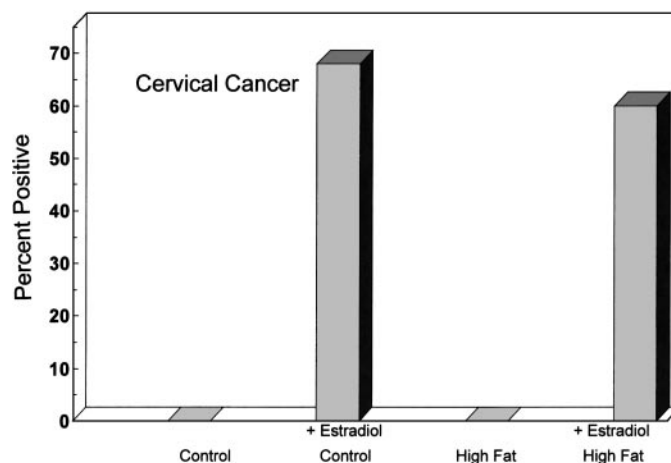


Fig. 4. Estrogen, but not *n*-6-PUFAs, increases cervical cancer in K14-HPV16 mice. Cervixes were harvested from the same mice and evaluated for cancer. The percentage of mice with invasive cervical cancer was compared in mice fed control or high-fat diets and treated or not treated with estradiol. Comparing the occurrence of cervical cancers in mice treated or not treated with estrogen, $P = 0.0002$ for groups given control diet or $P = 0.0002$ for groups given the high-fat diet. No difference was related to high-fat diet.

creases proliferation in breast cells *in vitro* (47, 48) and increases mammary tumors in mice (33, 34). In addition to tissue specificity, linoleic acid can promote UV-initiated skin cancer (14, 15) or inhibit certain chemically induced skin cancers (17–19) in various mouse models. An explanation for the tissue specificity of estrogen for cervical cancer is likely related to relative amounts of estrogen receptors. In estrogen-sensitive cells, estrogen increases proliferation, inhibits apoptosis, and is itself a carcinogen.

These studies shed additional information on the specificity of cofactors promoting cancers in HPV-infected cells. Most importantly, this study shows that the combination of HPV-expressing genes and high amounts of dietary *n*-6 fatty acids increases skin cancer.

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