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Cancer Epidemiol Biomarkers Prev 1995;4:437-440. Published online July 1, 1995.

Treatment with Human Chorionic Gonadotropin and Risk of Breast Cancer[1]

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Abstract

Studies of the induction of mammary tumors by 7,12-dimethlybenz(*a*)anthracene in a rat model show that human chorionic gonadotropin (hCG) administration reduces tumor incidence in a manner comparable to that of a completed pregnancy. On the basis of their studies, Russo and Russo (Cancer Epidemiol., Biomarkers & Prev., *3:* 353–364, 1994) have proposed that hCG treatment of young nulliparous women would reduce their breast cancer risk in a manner similar to that of a term pregnancy.

As part of a population-based, case-control study of breast cancer among women ages 40 years or younger, we asked women whether they had received hCG injections as part of a weight loss regimen or as a component of infertility treatment. Participants in this study were 744 women newly diagnosed with breast cancer between July 1983 and December 1988 and 744 controls individually matched on birthdate (within 36 months), race (white), parity (nulliparous/parous), and neighborhood of residence. Forty-five cases and 65 controls reported exposure to hCG (multivariate odds ratio = 0.77, 95% confidence interval = 0.50–1.19). Risk was reduced significantly among women whose maximum nonpregnant body mass index was less than 27.5 kg/m^2, but no reduction in risk was observed among more obese women. Although the odds ratios were reduced substantially for both nulliparous and parous women with maximum nonpregnant body mass indices less than 27.5, only the result for nulliparous women was statistically significant. These results are consistent with the effects proposed by Russo and Russo based on their animal model. Although not definitive, these results suggest that hCG may be a means for reducing breast cancer risk.

Received 1/4/95; revised 4/17/95; accepted 4/20/95.

[1] This research was supported by National Cancer Institute Grants CA44546 and CA17054 and the California Public Health Foundation, subcontract 050-F-8709, which is supported by the California Department of Health Services as part of its statewide cancer-reporting program mandated by Health and Safety Code Sections 210 and 211.3.

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Introduction

In studying the induction of mammary tumors by DMBA[3] in a rat model, Russo et al. (1) have shown that a term pregnancy induces permanent differentiation of terminal end buds into alveolar buds and lobules and results in substantial reduction in mammary tumor incidence. Moreover, these investigators have shown that treating young virgin rats with the placental hormone hCG mimics this protective, differentiating effect of a term pregnancy, reducing mammary carcinoma incidence in a dose-dependent manner (2). On the basis of these observations, Russo and Russo (3) have proposed that hCG treatment of young, nulliparous women would reduce breast cancer risk in a manner similar to that of a term pregnancy, thus providing a possible approach for preventing breast cancer.

Currently, the only clinical indication for hCG use is as part of a combination infertility treatment (with either clomiphene or menotropins) in which the objective is to induce ovulation (4). Biologically, hCG mimics the actions of luteinizing hormone. For infertility treatment, 5,000–10,000 IU are given in 1 or 2 injections. Anecdotal evidence indicates that daily injections of hCG have also been used extensively in conjunction with a low-calorie diet in weight reduction programs, although no evidence exists to support the efficacy of such a regimen, and its use has been frequently criticized (4–9). In southern California, weight loss clinics using this regimen apparently gained popularity during the 1960s and 1970s.

In a population-based, case-control study of breast cancer among young women, we specifically asked participants whether they had any hCG exposures as part of weight-loss regimens or as part of treatment for infertility. We report here on the relationship of such exposures to the breast cancer risk of young women.

Materials and Methods

The design of this study has been described in detail previously (10). Briefly, cases were white female residents of Los Angeles County ages 40 years or younger diagnosed with first primary *in situ* or invasive breast cancer between July 1, 1983, and January 1, 1989. One neighborhood control was individually matched to each of the 744 interviewed cases on birthdate (within 36 months), race (white), and parity (nulliparous *versus* parous). Subject eligibility was limited to women born in the United States, Canada, or Europe.

In-person interviews were conducted with all subjects by the same female nurse-interviewer. Signed, informed consent was obtained from each subject, and study procedures were approved by the University of Southern California Research Committee, in accord with assurances approved by the United

[3] The abbreviations used are: DMBA, 7,12-dimethylbenz(*a*)anthracene; hCG, human chorionic gonadotropin; OR, odds ratio; CI, confidence interval; BMI, body mass index.

States Department of Health and Human Services. We obtained complete information on reproductive factors, oral contraceptive and other hormone use, and physical exercise activities up to the date of case's diagnosis for both cases and controls and imposed time restrictions on these variables during the statistical analysis. A reference date, defined as the month and year that was 12 months before the date of the diagnosis of the case, was assigned to each case-control pair. This date has been used as the cutoff date for information used in the analyses presented here. Women with a positive family history of breast cancer had a mother or sister who had been diagnosed with breast cancer.

The data were analyzed with the use of univariate and multivariate conditional logistic regression methods for individually matched case-control studies (11). Multivariate models included the following factors: age at menarche (<12, 12, 13, ≥14 years); family history of breast cancer (no, yes, adopted); age at first term pregnancy (<20, 20–24, 25–29, 30–34, ≥35); total months of oral contraceptive use (none, 1–48, 49–96, 97–144, ≥145); total term pregnancies (1, 2, 3, ≥4); total months of breast feeding (none, 1–6, 7–15, ≥16); and average hours per week of exercise during reproductive years (none, 0.1–0.7, 0.8–1.6, 1.7–3.7, ≥3.8). Because complete histories of exercise activity were collected for only 545 case-control pairs (10), the remaining 199 matched pairs were included in the multivariate analyses by coding their exercise activity the same (arbitrarily chosen to be the baseline category); this effectively eliminated their contribution to estimating an exercise effect. Similarly, because cases and controls were matched on parity, nulliparous women were included in the baseline category for age at first term pregnancy and number of term pregnancies. Relative risks were estimated by ORs with 95% CIs. Tests for trend were calculated across categories. All significance levels reported (P values) are two-sided.

Results

A total of 45 breast cancer cases (6.1%) and 65 controls (8.7%) reported having ever had hCG injections (multivariate OR = 0.77; 95% CI = 0.50–1.19) (Table 1). Three of the cases (2 parous, 1 nulliparous) and 5 of the controls (1 parous, 4 nulliparous) had been given hCG as part of treatment for infertility. The remaining cases and controls had received hCG injections as part of a weight loss regimen. Restricting the analysis to women who had only used hCG for weight loss treatment did not substantially alter these results (OR = 0.78, 95% CI = 0.49–1.24) and the eight women treated with hCG for infertility are included in all of the analyses that follow.

A nonsignificant reduction in breast cancer risk was observed among nulliparous women and among parous women who first used hCG after their first term pregnancy (Table 1). The reduction in risk appears to be greater among women who were older than 25 years when they first received the drug (test for homogeneity of ORs, $P = 0.11$). This effect was evident for both nulliparous and parous women, and the logistic regression fit of the interaction model was not significantly better than the fit of the model that ignored parity ($P = 0.76$). Recency of use (within 8 years of reference date *versus* earlier termination of use) appears to have had little differential effect on breast cancer risk (test for homogeneity of ORs, $P = 0.78$).

Because the majority of subjects had used hCG as part of a weight loss program, we evaluated breast cancer risk in relation to maximum nonpregnant body mass index [maximum BMI = maximum weight (kg)/height $(M)^2$]. As shown in Table 2, in multivariate analysis, breast cancer risk declined with increasing maximum BMI, although the results are not statistically significant. No effect was observed for BMI at the reference date (Table 2).

To examine the interaction between maximum nonpregnant BMI and use of hCG, women were categorized on maximum BMI (<27.5 or ≥27.5, a cutpoint that is approximately the upper quartile for control women and that is roughly equivalent to a 65-inch-tall woman weighing 165 pounds). Among women with a maximum BMI <27.5, we observed a significant protective effect of hCG use (multivariate OR = 0.42; 95% CI = 0.20–0.88; Table 3). Among women with a maximum BMI of at least 27.5, the ORs for breast cancer (relative to nonusers of hCG with a maximum BMI <27.5) were similar among users and nonusers of hCG. Further examination of this relationship by parity status shows that the ORs for breast cancer associated with hCG use were reduced among both nulliparous and parous women whose maximum BMI was <27.5; the result for nulliparous women was statistically significant. The fit of this logistic regression model with separate terms for nulliparous and parous women was not significantly better than that of the model that ignored parity ($P = 0.80$).

Table 1 Crude and adjusted relative odds of breast cancer associated with exposure to hCG

Factor	No. cases/ controls	Odds ratios (95% confidence intervals)	
		Crude	Multivariate adjusted[a]
HCG use			
Never	699/679	1.0	1.0
Ever	45/65	0.67 (0.45–0.999)	0.77 (0.50–1.19)
Timing of first hCG use in relation to first term pregnancy[b]			
Nulliparous			
Never	259/248	1.0	1.0
Ever	15/26	0.54 (0.28–1.06)	0.70 (0.34–1.42)
Parous			
Never	440/431	1.0	1.0
Before	11/10	1.06 (0.45–2.50)	1.17 (0.46–2.90)
After	19/29	0.66 (0.39–1.17)	0.73 (0.37–1.38)
Age at first use (yr)			
No use	699/679	1.0	1.0
≤25	26/30	0.84 (0.49–1.42)	1.07 (0.60–1.92)
>25	19/35	0.52 (0.30–0.93)	0.55 (0.30–1.02)
Nulliparous[b] (yr)			
Never	259/248	1.0	1.0
≤25	8/12	0.62 (0.25–1.53)	0.82 (0.32–2.16)
>25	7/14	0.48 (0.19–1.19)	0.60 (0.23–1.54)
Parous[b] (yr)			
Never	440/431	1.0	1.0
≤25	18/18	0.98 (0.51–1.89)	1.25 (0.60–2.59)
>25	12/21	0.55 (0.26–1.15)	0.52 (0.23–1.17)
Years since last use			
Never	699/679	1.0	1.0
≤8	20/28	0.70 (0.39–1.24)	0.73 (0.39–1.36)
>8	25/37	0.65 (0.39–1.10)	0.82 (0.46–1.46)

[a] Models include adjustment for first-degree family history of breast cancer (mother or sister), age at menarche, age at first term pregnancy, total term pregnancies, months of lactation, months of oral contraceptive use, average hours of exercise per week during reproductive years, and maximum nonpregnant body mass index = [maximum weight (kg)/height $(M)^2$].
[b] Logistic regression model simultaneously fits data for nulliparous and parous women.

Table 2 Crude and adjusted relative odds of breast cancer associated with maximum nonpregnant body mass index [maximum weight (kg)/height $(M)^2$] and body mass index at reference date [weight at reference date (kg)/height $(M)^2$]

Factor	No. Cases/ controls	Odds ratios (95% confidence intervals)	
		Crude	Multivariate adjusted[a]
Maximum BMI			
≤21.9	200/186	1.0	1.0
22.0–23.9	168/176	0.89 (0.66–1.18)	0.87 (0.64–1.19)
24.0–27.4	196/192	0.95 (0.72–1.25)	0.89 (0.66–1.21)
≥27.5	180/190	0.88 (0.66–1.17)	0.76 (0.55–1.06)
		Test for trend, $P = 0.15$	
BMI at reference date			
≤20.2	173/186	1.0	1.0
20.3–22.0	211/196	1.15 (0.87–1.52)	1.21 (0.90–1.63)
22.1–24.9	184/180	1.10 (0.82–1.47)	1.04 (0.76–1.42)
≥25.0	176/182	1.04 (0.77–1.39)	0.96 (0.69–1.34)
		Test for trend, $P = 0.64$	

[a] Models include adjustment for first-degree family history of breast cancer (mother or sister), age at menarche, age at first term pregnancy, total term pregnancies, months of lactation, months of oral contraceptive use, average hours of exercise per week during reproductive years, and ever use of hCG.

Table 3 Assessment of the relative odds of breast cancer associated with exposure to hCG in relation to maximum nonpregnant body mass index [maximum weight (kg)/height $(M)^2$] and parity status

Interaction between maximum nonpregnant BMI and hCG use	No. Cases/ controls	Odds ratios (95% confidence intervals)	
		Crude	Multivariate adjusted[b]
All women			
Maximum BMI ≤27.4			
Never used hCG	552/525	1.0	1.0
Ever used hCG	12/29	0.38 (0.19–0.77)	0.42 (0.20–0.88)
Maximum BMI ≥27.5			
Never used hCG	147/154	0.91 (0.70–1.17)	0.77 (0.58–1.02)
Ever used hCG	33/36	0.88 (0.54–1.43)	0.88 (0.51–1.50)
Nulliparous women[b]			
Maximum BMI ≤27.4			
Never used hCG	211/200	1.0	1.0
Ever used hCG	4/15	0.26 (0.09–0.79)	0.30 (0.10–0.96)
Maximum BMI ≥27.5			
Never used hCG	48/48	0.93 (0.60–1.45)	0.81 (0.50–1.29)
Ever used hCG	11/11	0.97 (0.38–2.49)	1.12 (0.42–3.02)
Parous women[b]			
Maximum BMI ≤27.4			
Never used hCG	341/325	1.0	1.0
Ever used hCG	8/14	0.53 (0.21–1.32)	0.55 (0.20–1.49)
Maximum BMI ≥27.5			
Never used hCG	99/106	0.90 (0.65–1.23)	0.75 (0.53–1.06)
Ever used hCG	22/25	0.85 (0.48–1.51)	0.80 (0.42–1.52)

[a] Models include adjustment for first-degree family history of breast cancer (mother or sister), age at menarche, age at first term pregnancy, total term pregnancies, months of lactation, months of oral contraceptive use, and average hours of exercise per week during reproductive years.
[b] Logistic regression model simultaneously fits data for nulliparous and parous women.

Discussion

In their series of studies on mammary carcinogenesis in a rat model, Russo *et al.* (1) have established that a term pregnancy results in substantial protection against DMBA-induced malignant transformation. This is likely mediated through permanent structural changes consisting of complete differentiation of terminal end buds. In this model, when DMBA is administered to parous rats, both the number of animals with mammary tumors and the number of tumors per affected animal are markedly lower than that observed in virgin rats (1).

hCG, which is structurally similar to chorionic gonadotropin produced by the placenta of rats and other rodents (12), exerts a similar dose-dependent protective effect on mammary carcinogenesis (2). In an experiment in which virgin rats were treated with hCG at doses of 1, 10, or 100 IU daily for 21 days (the length of a pregnancy), followed by a 21-day rest period and then administration of DMBA, a dramatic dose-dependent decline in tumor incidence was observed. The 44% incidence of adenocarcinomas among rats not receiving any hCG was decreased to 34% among those treated with 1 IU, 18% among those treated with 10 IU, and 6% among those treated with 100 IU. The reduction in incidence achieved at the highest dose was similar to that achieved by completed pregnancy with the use of the same animal model (1, 2). It is important that hCG did not stimulate the growth of initiated tumors in this animal model (2). In fact, hCG treatment at 100 IU initiated 21 days after DMBA exposure reduced tumor incidence by more than 50% (2, 3).

In the United States and elsewhere, hCG injections have been used in conjunction with a low-calorie diet with the aim of achieving substantial weight reduction despite the lack of supportive evidence on the efficacy of such a regimen (6, 7, 9). In these regimens, adopted by a group of "weight clinics" in the United States, a relatively low dose of hCG is administered, and the duration of therapy ranges from several weeks to many months (5, 8). The original regimen, known as the "Simeons regimen," consisted of a series of i.m. injections of 125 IU of hCG given 6 times/week for 7 weeks (40 injections total; Ref. 13). Simeons proposed that these injections would lead to better adherence to a 500 calorie/day diet, fewer symptoms during the period of food restriction, and enhanced loss of "abnormal" or "reserve" (*versus* "normal" or "structural") fat (13). The fact that this regimen had been used, and that weight-loss clinics flourished in southern California (14), allowed us to do a preliminary assessment of the effects of hCG on the breast cancer risk of young women. Our results, showing a statistically significant reduction in breast cancer risk associated with hCG use among women with maximum nonpregnant BMI below that of the 75th percentile for controls, are consistent with the effects proposed by Russo and Russo (3) based on their animal model. This protective effect was more pronounced among nulliparous women than among parous women as they have suggested it should be.

The apparent interaction of hCG use with obesity may be due to chance. We had no *a priori* hypotheses regarding such an effect. A possible alternative interpretation of this lack of an effect among relatively "obese" women could be that they received a relatively low effective daily dose (125 IU as a function of kg of body weight) of hCG. On the basis of our data, the effect was more apparent among women whose first use was in their late 20s or 30s. We have no explanation for this finding. Because the prevalence of exposure in our study population was relatively low (8.7% among controls), we were unable to examine the effects of age at first use and latency or, for that matter, any other possible effect modifiers in great detail. Furthermore, we unfortunately did not collect data on the total number of injections received by women who received

hCG shots as part of a weight loss program, so we were unable to estimate dose-response relationships.

Although our data are hardly definitive, they do suggest that hCG might reduce breast cancer risk, consistent with a well established animal model of this disease. The protective influence of a term pregnancy on breast cancer risk is well known and highly reproducible, but establishing the mechanism has proved elusive. Although we and others have suggested that part of this effect might be mediated through a permanent reduction in circulating estrogen and prolactin levels (15–17), hormonally mediated terminal differentiation of mammary epithelium has also been proposed (18). This study suggests that hCG might play a role in inducing this differentiation and, as a result, in reducing breast cancer risk.

Acknowledgments

We want to express our gratitude to all of the women who participated in this study and to the physicians who allowed us to contact their patients.

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