Short Communication

Oral Contraceptive Use and Cyclin D1 Overexpression in Breast Cancer among Young Women

Mary Beth Terry,[1] Marilie D. Gammon, Janet B. Schoenberg, Louise A. Brinton, Nadir Arber, and Hanina Hibshoosh

Department of Epidemiology, Mailman School of Public Health [M. B. T.], Herbert Irving Comprehensive Cancer Center [M. B. T., H. H.], and Department of Pathology, College of Physicians and Surgeons [H. H.], Columbia University, New York, New York 10032; Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina 27599-7345 [M. D. G.]; New Jersey State Department of Health and Senior Services, Cancer Epidemiology Services, Trenton, New Jersey 08625-0369 [J. B. S]; National Cancer Institute, Environmental Epidemiology Branch, Bethesda, Maryland 20892-7234 [L. A. B.]; and Department of Gastroenterology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel 55454 [N. A.]

Abstract

Cyclin D1, an important cell cycle regulator, is overexpressed in several human cancers including breast. Both estrogens and progestins activate the transcription of the gene; antiestrogens have been shown to reduce cyclin D1 protein levels. Cyclin D1 protein overexpression has been strongly associated with well-differentiated, estrogen receptor-positive tumors. Little is known, however, as to whether epidemiological risk factors are related to this molecularly defined subset of tumors. Using a population-based study of young women <45 years in New Jersey, we analyzed whether oral contraceptives (OCs) and other risk factors were associated with the overexpression of cyclin D1 in breast cancer tissue. We measured cyclin D1 status in paraffin-embedded, archived tissue from 78.8% of the breast cancer cases using immunohistochemistry. Cyclin D1 was overexpressed in 33.7% of the cases (123 of 365). We used unordered polytomous logistic regression to estimate the odds ratios (ORs) for two case groups—(*a*) breast cancer with cyclin D1 overexpression ($n = 123$) and (*b*) breast cancer without overexpression ($n = 242$)—compared with 462 population-based controls. The multivariate-adjusted OR for ever use of OCs was 1.6 [95% confidence interval (CI), 1.0–2.5] for cases that overexpressed cyclin D1 and 1.0 (95% CI, 0.7–1.5) for those with no overexpression. Among women who started using OCs at least 20 years before the reference date, the OR was increased 2-fold for breast cancer with cyclin D1 overexpression (OR, 2.2; 95% CI, 1.2–4.0) but not for breast cancer without cyclin D1 overexpression (OR, 1.1; 95% CI, 0.7–1.8). If replicated, these findings suggest that early OC use may be associated with the subset of mammary tumors that overexpress cyclin D1.

Introduction

Cyclin D1, an important cell cycle regulator located on chromosome 11q13, is overexpressed in several human cancers including esophageal, squamous head and neck, non-small cell lung, hepatocellular, bladder, colon, prostate, and breast (1–8). Cyclin D1, along with cyclin E and their associated cyclin-dependent kinases, phosphorylate the Rb[2] protein, thus preventing Rb from performing its inhibitory role in the cell cycle (2, 9). When cyclin D1 protein is overexpressed in a cell, phosphorylated Rb does not prevent the cell from passing through the cell cycle, and cell replication continues to the S-phase (9, 10).

In the breast, cyclin D1 protein plays a role in both normal mammary development and malignant transformation (3, 11). In particular, alterations in the *cyclin D1* gene may be a fundamental and early step in breast cancer progression (12, 13). Cyclin D1 overexpression has been strongly associated with well-differentiated, estrogen receptor-positive tumors (1). Both estrogens and progestins activate the transcription of the gene (13, 14–17). These steroid hormones and their interplay with cyclin D1 recruit noncycling cells into the cell cycle and shorten the overall cell cycle time by reducing the length of G_1 (14, 18–20). In addition, many other lines of evidence support the relationship between hormones and cyclin D1: antiestrogens have been shown to reduce cyclin D1 protein levels in estrogen receptor-positive breast cancer cell lines (13, 21); pregnancy-induced changes in mammary tissues do not occur in cyclin D1 knockout mice (5, 9, 22, 23); and transgenic mice that are bred with additional cyclin D1 have increased mammary hyperplasia (17, 24).

Little is known, however, as to whether breast cancer risk factors are associated with the subset of tumors that overexpress cyclin D1. In particular, we were interested in whether use of exogenous estrogens, such as OCs, is associated with tumors that overexpress cyclin D1. Using a population-based study of young women <45 years in New Jersey, we undertook a study to examine whether OCs and other risk factors were associated with the overexpression of cyclin D1 in breast cancer tissue.

Sujects and Methods

Study Population. This study builds on information collected as part of a large multicenter, population-based case-control study (25). The cases and controls are derived from the New Jersey site of the parent study (26). Cases were women who were characterized as follows: diagnosed with *in situ* and in-

Received 9/21/01; revised 5/24/02; accepted 5/30/02.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] To whom requests for reprints should be addressed, at Department of Epidemiology, Mailman School of Public Health, 600 West 168th Street, PH 18-102, Columbia University, New York, New York 10032.

[2] The abbreviations used are: Rb, retinoblastoma; OC, oral contraceptive; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

Table 1 Demographic and tumor characteristics of breast cancer cases and controls by cyclin D1 status among young women <45 years of age in New Jersey from 1990 to 1992

	Cyclin D1^{+a} *n* (%)	Cyclin D1^{-b} *n* (%)	Controls^{c} *n* (%)	*P*
Age (yrs) at diagnosis	38.91 (4.28)^{d}	38.83 (4.36)^{d}	37.75 (4.80)^{d}	0.003
23–29 yr	3 (2.44)	10 (4.13)	27 (5.84)	0.21
30–34 yr	18 (14.63)	35 (14.46)	83 (17.97)	
35–39 yr	36 (28.10)	68 (28.10)	147 (31.82)	
40–44 yr	66 (53.31)	129 (53.31)	205 (44.37)	
Stage at diagnosis				
In situ	15 (12.30)	27 (11.34)		0.62
Local	57 (46.72)	124 (52.10)		
Regional/Distant	50 (40.98)	87 (36.55)		
ER status				0.01
No test or unknown	24 (19.51)	30 (12.40)		
Positive	69 (56.10)	99 (40.91)		
Borderline	12 (9.76)	18 (7.44)		
Negative	18 (14.63)	95 (39.26)		
Progesterone receptor status				0.001
No test or unknown	25 (20.33)	37 (15.29)		
Positive	72 (58.54)	109 (45.04)		
Borderline	4 (3.25)	13 (5.37)		
Negative	22 (17.89)	83 (34.30)		
Race				
White	108 (87.80)	201 (83.06)	382 (82.68)	0.34
Black	8 (6.50)	30 (12.40)	48 (10.39)	
Asian and other	7 (5.69)	11 (4.55)	32 (6.93)	
Religion				
Protestant	39 (31.71)	77 (31.82)	154 (33.33)	0.52
Jewish	15 (12.20)	21 (8.68)	46 (9.96)	
Catholic	65 (52.85)	138 (57.02)	238 (51.52)	
Other/None	4 (3.25)	6 (2.48)	24 (5.19)	

[a] $N = 123$.
[b] $N = 242$.
[c] $N = 462$.
[d] Mean (SD).

vasive breast cancer between May 1, 1990 and December 31, 1992; between the ages of 20 to 44 years at diagnosis; and lived in a five-county study area in New Jersey (Middlesex, Monmouth, Morris, Somerset, and Union). Controls were women without breast cancer, were between the ages of 20 to 44, and who lived in the same five-county area. Cases were identified through rapid reporting; controls were identified through random digit dialing (27).

Questionnaire Data. Interviews were completed for 509 cases (83.4% of eligible cases) and 462 controls (76.9% of eligible controls). The in-person interview included determination of OC use (using reproductive and contraceptive calendars); menstrual and reproductive histories including pregnancies, lactation, and abortions; lifetime alcohol consumption patterns; adolescent diet; body size and development; physical activity; demographic factors; family history of cancer; and medical history including biopsy-proven benign breast disease and gynecological surgery. Subjects were also requested to complete a self-administered food frequency questionnaire.

Block Retrieval. We retrieved paraffin-embedded tissue blocks for 401 (78.8%) of the breast cancer cases. As reported previously (26), there were no statistically significant differences between the distribution of known and suspected breast cancer risk factors for cases with tumor tissue available and those without tumor tissue available.

Immunohistochemistry. We performed immunohistochemistry (1, 6) using 5 μm of formalin-fixed, paraffin-embedded tissue sections, placing them on silane-coated slides, and baking them at 60°C for 30 min. Afterward, the slides were deparaffinized, hydrated, placed in 10 mM citrate buffer (pH 6), and microwaved for a total of 10 min (antigen retrieval). Appropriate blocking serum (horse serum) and an anti-cyclin D1 (Immunotech 1:20) monoclonal mouse IgG2a antibody was used. The detection method used Vectastain, Elite ABC kit (Vector Laboratories, Burlingame, CA). Chromagen diaminobenzidine) was used, and sections were counterstained with methyl green (Ethyl Green; Sigma Chemical Co., St. Louis, MO).

The study pathologist (H. H.), blinded to case status, reviewed the stained slides and scored each case based on staining intensity and percentage of nuclei showing evidence of overexpression. The following categories were used for scoring: intensity (none, mild, moderate, and strong); and percentage of positive nuclear staining (none or rare; <10%; 10–25%; 25–50%; and >50%). Categories reflect levels of staining not observed in normal tissue of the breast. Cases were classified as: positive (cyclin D1^{+}) if the intensity score was moderate or strong and at least 10% or more of cells showed evidence of overexpression; and negative (cyclin D1^{-}) if the intensity score was none or mild or <10% of cells in showed evidence of overexpression. Cyclin D1 status was successfully determined for 365 cases (91%); the remaining 9% had too little tissue available for analysis.

Statistical Methods. For univariate analyses, we used χ^2 tests to evaluate differences in characteristics by cyclin D1 status. For multivariate analyses, we used unordered polytomous logistic re-

gression models to adjust for potential confounding variables (28). There were a total of three outcome categories: (*a*) cyclin $D1^+$ cases; (*b*) cyclin $D1^-$ cases; and (*c*) controls. Comparisons were made using ORs and 95% CIs for cyclin $D1^+$ cases *versus* controls, cyclin $D1^-$ cases *versus* controls, and cyclin $D1^+$ *versus* cyclin $D1^-$ cases. We examined differences across cyclin D1 status by examining the OR of cyclin $D1^+$ cases compared with cyclin $D1^-$ cases (which is equivalent to exponentiation of the difference in the β coefficients in a model using controls) and the 95% CI (based on the variance for the difference in the beta coefficients; see Ref. 28). After estimating associations based on the *a priori* cutoffs described above for cyclin D1 status, we performed sensitivity analyses to examine whether altering the cutoffs changed the overall results.

Results

Cyclin D1 was overexpressed in 33.7% of the breast cancer cases (123 of 365). Table 1 reports the distribution of demographic and tumor characteristics for breast cancer cases and controls by cyclin D1 status. Cases with cyclin D1 overexpression were more likely to have ER-positive tumors (56% of cyclin $D1^+$ cases were ER positive compared with 41% of cyclin $D1^-$ cases) and PR-positive tumors (59% of cyclin $D1^+$ cases were PR positive compared with 45% of cyclin $D1^-$ cases). There were no differences in cyclin D1 status by age, stage at diagnosis, race, or religion.

The multivariate-adjusted OR for ever use of OCs was 1.6 (95% CI, 1.0–2.5) for cases that overexpressed cyclin D1 and 1.0 (95% CI, 0.7–1.5) for those with no overexpression (see Table 2). Among women who started using OCs at least 20 years before the reference date, the OR was increased 2-fold for breast cancer with cyclin D1 overexpression (2.2; 95% CI, 1.2–4.0) but not for breast cancer without cyclin D1 overexpression (OR, 1.1; 95% CI, 0.7–1.8). The OR for OC use at least 20 years before the reference date for cyclin $D1^+$ *versus* cyclin $D1^-$ cancer was statistically significant (OR, 2.0; 95% CI, 1.1–3.7). The risk from OCs did not differ whether use started before or after the first full-term pregnancy (data not shown). We also analyzed whether the association between OC use and cyclin D1 status was altered by ER status. The OR for any use of OCs for cyclin $D1^+$ overexpression was stronger in ER-negative cases (2.5; 95% CI, 0.7–9.3) than in ER-positive cases (OR, 1.3; 95% CI, 0.7–2.3).

Table 2 also reports associations between other exposures and cyclin D1 status. Consumption of seven or more alcoholic drinks/week was only modestly associated with cyclin $D1^-$ breast cancer and not statistically significant. The association with first-degree family history of breast cancer was lower among cyclin $D1^+$ cases (OR, 1.6; 95% CI, 0.8–3.3) than for cyclin $D1^-$ cases (OR, 2.6; 95% CI, 1.5–4.3), but the case/case difference was not markedly different (OR, 0.6; 95% CI, 0.3–1.2). Prior breast biopsy was associated with breast cancer risk, irrespective of cyclin D1 status.

Sensitivity analyses altering the cutoff for cyclin D1 positivity—(*a*) liberally, by including those with moderate staining and <10% of cells positive, and (*b*) conservatively, by excluding those with percent positive <25%—did not lead to different interpretations. We also examined whether the associations we found with early OC use could be explained by *Her2/neu* status. There was no association between *Her2/neu* status and cyclin D1 status in these data (37.2% of the cyclin $D1^+$ subjects also overexpressed *Her2/neu* compared with 45.4% of the cyclin $D1^-$ subjects).

Table 2 Multivariate adjusted[a] ORs and 95% CIs for cyclin D1 status among women <45 years of age in New Jersey from 1990 to 1992

	Cyclin $D1^+$ *vs.* controls	Cyclin $D1^-$ *vs.* controls	Cyclin $D1^+$ *vs.* cyclin $D1^-$
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Ever use of OCs			
Never	1.0	1.0	
Ever	1.57 (1.0–2.49)	1.04 (0.74–1.48)	1.50 (0.92–2.47)
No. of years since first use of OC (yr)			
Never users	1.0	1.0	
<15	1.44 (0.72–2.89)	1.14 (0.66–1.98)	1.26 (0.59–2.69)
15–19	1.08 (0.59–1.96)	0.92 (0.60–1.44)	1.16 (0.61–2.12)
≥20	2.23 (1.24–4.01)	1.10 (0.70–1.76)	2.01 (1.08–3.74)
Alcohol intake (drinks/week)			
None	1.0	1.0	
<7	0.85 (0.54–1.32)	1.05 (0.73–1.49)	0.81 (0.50–1.32)
≥7	0.66 (0.28–1.55)	1.31 (0.73–2.38)	0.50 (0.21–1.21)
Age at first birth (for each additional yr relative to mean)	1.06 (1.00–1.11)	1.03 (0.99–1.07)	1.03 (0.98–1.08)
Parous Ever	1.0	1.0	
Never	1.12 (0.66–1.91)	1.11 (0.73–1.69)	1.01 (0.57–1.80)
Age at menarche (yr)			
8–12	1.0	1.0	
13+	0.73 (0.48–1.10)	0.74 (0.53–1.03)	0.98 (0.62–1.53)
Family history			
None	1.0	1.0	
First-degree relatives	1.60 (0.79–3.25)	2.55 (1.52–4.28)	0.63 (0.32–1.24)
Prior breast biopsy			
No	1.0	1.0	
Yes	3.49 (1.68–7.27)	2.52 (1.32–4.83)	1.39 (0.68–2.82)
Caloric intake (kcal, in quartiles)			
<1100	1.0	1.0	
1100–1450	1.36 (0.76–2.44)	1.48 (0.91–2.39)	0.92 (0.48–1.75)
1450–1830	0.95 (0.50–1.78)	1.34 (0.82–2.18)	0.71 (0.36–1.42)
≥1830	1.49 (0.82–2.70)	2.01 (1.24–3.23)	0.74 (0.39–1.42)

[a] Adjusted for all other variables in the table.

Discussion

We found an overall prevalence of cyclin D1 overexpression of 33.7%. This estimate is similar to other studies that report a range of 30–45% of breast tumors (1, 2, 23), although other estimates are higher at 60–80% (3–5, 12). Similar to others (1), we have also found that cyclin D1 overexpression is strongly associated with ER-positive tumors. We also found that cyclin D1 is associated with PR positivity.

We found that most risk factors for breast cancer did not differ by cyclin D1 status. However, OC use, particularly first use ≥20 years before diagnosis, was more likely to be associated with tumors that overexpressed cyclin D1 protein than those that did not. This finding is consistent with laboratory data suggesting that estrogens can activate transcription of the cyclin D1 gene (13, 15, 16). The heterogeneity in risk estimates that we found (ORs for cyclin $D1^+$ ranging from 1.5 to 2.0 and the ORs for cyclin $D1^-$ of ~1.0) also is consistent with previous reports (25, 29) of a modest effect (20–30%) of OC use and breast cancer risk (ever use in the parent study: OR, 1.3; 95% CI, 1.1–1.5). We had reported previously an association between early OC use and Her2/neu protein overexpression in the same study population (30). The lack of association between cyclin D1 status and Her2/neu status suggests two distinct pathways for OC action in altering breast tissue markers.

The dependent variable we used in the regression models was

a three-level variable (cyclin $D1^+$, cyclin $D1^-$, and controls). This type of modeling has an advantage over case/case because a risk factor may be positively associated (OR >1.0) for cases with the marker and negatively associated (OR < 1.0) for cases without the marker (or *vice versa*) relative to controls, and case/case analyses do not reveal these differences. Polytomous outcome variables require consideration of all pair-wise misclassification patterns because not all comparisons will be attenuated (31). If the risk factor is associated monotonically with disease (marker-positive cases have a greater risk than marker-negative cases), associations between the marker-positive cases and controls will be biased toward the null, and associations between the marker negative cases and controls will be biased away from the null. Case/case analyses will therefore be biased toward the null. Thus, measurement error in the outcome variable cannot explain the 2-fold association between early OC use and cyclin $D1^+$ tumors as compared with cyclin $D1^-$ tumors, and the true association is likely to be larger.

Recall bias is also unlikely to provide an alternative explanation for our findings because although it is possible that OC use and other exposure information was differentially recalled by cases and controls, it is unlikely that such misclassification would differ by cyclin D1 status. Selection bias is also unlikely to explain the results because there were no differences between subjects who had paraffin-embedded tissue blocks available for analyses and those who did not (see Ref. 26 for detailed comparisons). Although it is possible that there were differences between subjects who participated in the parent study and those who did not, it is unlikely that those who participated differed in terms of cyclin D1 status from those who did not participate. We also considered confounding by other risk factors as an explanation for the findings. In multivariate models, we considered joint confounding by sets of risk factors. We were able to consider a range of confounders because the parent study questionnaire was very comprehensive (25). It is possible that there was unmeasured confounding; however, a confounder would have to differ by both cyclin D1 status and OC use to explain the results presented in this report.

In conclusion, we found that early contraceptive use was more likely to be associated with cyclin $D1^+$ cancer than with cyclin $D1^-$ cancer. There is no strong evidence that measurement error, recall bias, selection bias, and/or confounding could have accounted for these findings. If replicated, these findings suggest that early OC use may be associated with a subset of mammary tumors that overexpress cyclin D1.

References

1. Gillett, C., Fantl, V., Smith, R., Fisher, C., Bartek, J., Dickson, C., Barnes, D., and Peters, G. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Cancer Res., *54:* 1812–1817, 1994.
2. Weinstein, I. B. Relevance of cyclin D1 and other molecular markers to cancer chemoprevention. J. Cell. Biochem. Suppl., *25:* 23–28, 1996.
3. Lamb, J., Ladha, M. H., McMahon, C., Sutherland, R. L., and Ewen, M. E. Regulation of the functional interaction between cyclin D1 and the estrogen receptor. Mol. Cell Biol., *20:* 8667–8675, 2000.
4. Zhang, S., Caamano, J., Cooper, F., Guo, X., and Klein-Szanto, A. J. P. Immunohistochemistry of cyclin D1 in human breast cancer. Am. J. Clin. Pathol., *102:* 695–698, 1994.
5. Bartkova, J., Lukas, J., Muller, H., Lutzhoft, D., Strauss, M., and Bartek, J. Cyclin D1 protein expression and function in human breast cancer. Int. J. Cancer, *57:* 353–361, 1994.
6. Arber, N., Gammon, M. D., Hibshoosh, H., Britton, J. A., Zhang, Y., Schonberg, J. B., Roterdam, H., Fabian, I., Holt, P. R., and Weinstein, I. B. Overexpression of cyclin D1 occurs in both squamous carcinomas and adenocarcinomas of the esophagus and in the adenocarcinomas of the stomach. Hum. Pathol., *30:* 1087–1092, 1999.
7. Sutter, T., Doi, S., Carnevale, K. A., Arber, N., and Weinstein, I. B. Expressions of cyclins D1 and E in human colon adenocarcinomas. J. Med., *28:* 285–301, 1997.
8. Han, E. K. H., Rubin, M. A., Lim, T., Arber, N., Xing, W. Q., and Weinstein, I. B. Cyclin D1 expression in human prostate carcinoma cell lines and primary tumors. Prostate, *35:* 95–101, 1998.
9. Barnes, D. M. Cyclin D1 in mammary carcinoma. J. Pathol., *181:* 267–269, 1997.
10. Jiang, W., Kahn, S. M., Zhou, P., Zhang, Y., Cacace, A. M., Infante, A. S., Doi, S., Santella, R. M., and Weinstein, I. B. Overexpression of cyclin D1 in rat fibroblasts causes abnormalities in growth control, cell cycle progression and gene expression. Oncogene, *8:* 3447–3457, 1993.
11. Sicinski, P., and Weinberg, R. A. A specific role for cyclin D1 in mammary gland development. J. Mammary Gland Biol. Neoplasia, *2:* 335–342, 1997.
12. Weinstat-Saslow, D., Merino, M. J., Manrow, R. E., Lawrence, J. A., Bluth, R. F., Wittenbel, K. D., Simpson, J. F., Page, D. L., and Steeg, P. S. Overexpression of cyclin D mRNA distinguishes invasive and *in situ* breast carcinomas from non-malignant lesions. Nat. Med., *1:* 1257–1260, 1995.
13. Sutherland, R. L., Hamilton, J. A., Sweeney, K. J. A., Watts, C. K. W., and Musgrove, E. A. Expression and regulation of cyclin genes in breast cancer. Acta Oncol., *34:* 651–656, 1995.
14. Musgrove, E. A., and Sutherland, R. L. Cell cycle control by steroid hormones. Semin. Cancer Biol., *5:* 381–389, 1994.
15. Foster, J. S., and Wimalasena, J. Estrogen regulates activity of cyclin-dependent kinases and retinoblastoma protein phosphorylation in breast cancer cells. Mol. Endocrinol., *10:* 488–498, 1996.
16. Altucci, L., Addeo, R., Cicatiello, L., Dauvois, S., Parker, M. G., Truss, M., Beato, M., Sica, V., Bresciani, F., and Weisz, A. 17β-Estradiol induces cyclin D1 gene transcription, p36D1–p34cdk4 complex activation and p105Rb phosphorylation during mitogenic stimulation of G(1)-arrested human breast cancer cells. Oncogene, *12:* 2315–2324, 1996.
17. Steeg, P. S., and Zhou, Q. Cyclins and breast cancer. Breast Cancer Res. Treat., *52:* 17–28, 1998.
18. Sutherland, R. L., Prall, O. W., Watts, C. K., and Musgrove, E. A. Estrogen and progestin regulation of cell cycle progression. J. Mammary Gland Biol. Neoplasia, *3:* 63–72, 1998.
19. Foster, J. S., Henley, D. C., Bukovsky, A., Seth, P., and Wimalasena, J. Multifaceted regulation of cell cycle progression by estrogen L regulation of Cdk inhibitors and Cdc25A independent of cyclin D1-Cdk4 function. Mol. Cell. Biol., *21:* 794–810, 2001.
20. Prall, O. W., Rogan, E. M., and Sutherland, R. L. Estrogen regulation of cell cycle progression in breast cancer cells. J. Steroid Biochem. Mol. Biol., *65:* 169–174, 1998.
21. Watts, C. K. W., Sweeney, K. J. E., Warlters, A., Musgrove, E. A., and Sutherland, R. L. Antiestogen regulation of cell cycle progression and cyclin D1 gene expression in MCF-7 human breast cancer cells. Breast Cancer Res. Treat., *31:* 95–105, 1994.
22. Sicinski, P., Donaher, J. L., Parker, S. B., Li, T., Fazeli, A., Gardner, H., Haslam, S. Z., Bronson, R. T., Elledge, S. J., and Weinberg, R. A. Cyclin D1 provides a link between development and oncogenesis in the retina and breast. Cell, *82:* 621–630, 1995.
23. Schmidt, E. V. Happenstance, circumstance or enemy action: cyclin D1 in breast, eye and brain. Bioessays, *18:* 6–8, 1996.
24. Wang, T. C., Cardiff, R. D., Zukerberg, L., Lees, E., Arnold, A., and Schmidt, E. B. Mammary hyperplasia and carcinoma in MMTV-cyclin D1 transgenic mice. Nature (Lond.), *369:* 669–671, 1994.
25. Brinton, L. A., Daling, J. R., Liff, J. M., Schoenberg, J. B., Malone, K. E., Stanford, J. L., Coates, R. J., Gammon, M. D., Hanson, L., and Hoover, R. N. Oral contraceptives and breast cancer risk among younger women. J. Natl. Cancer Inst., *87:* 827–835, 1995.
26. Gammon, M. D., Hibshoosh, H., Terry, M. B., Bose, S., Schoenberg, J. B., Brinton, L. A., Bernstein, J. L., and Thompson, W. D. Cigarette smoking and other risk factors in relation to p53 expression in breast cancer among young women. Cancer Epidemiol. Biomark. Prev., *8:* 255–263, 1999.
27. Waksberg, J. Sampling methods for random digit dialing. J. Am. Stat. Assoc., *73:* 40–46, 1978.
28. Hosmer, D. W., and Lemeshow, S. Applied Logistic Regression. New York: John Wiley & Sons, 1989, 216–238.
29. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53, 297 women with breast cancer and 100, 239 women without breast cancer from 54 epidemiological studies. Lancet, *347:* 1713–1727, 1996.
30. Gammon, M. D., Hibshoosh, H., Terry, M. B., Bose, S., Schoenberg, J. B., Brinton, L. A., Bernstein, J. L., and Thompson, W. D. Oral contraceptive use and other risk factors in relation to HER-2/neu overexpression in breast cancer among young women. Cancer Epidemiol. Biomark. Prev., *8:* 413–419, 1999.
31. Terry, M. B., Gammon, M. D., Ng-Mak, D., and Thompson, W. D. Re: "p53 protein overexpression in relation to risk factors for breast cancer". Am. J. Epidemiol., *147:* 511–512, 1998.

Oral Contraceptive Use and Cyclin D1 Overexpression in Breast Cancer among Young Women

Mary Beth Terry, Marilie D. Gammon, Janet B. Schoenberg, et al.

Cancer Epidemiol Biomarkers Prev 2002;11:1100-1103.