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Thomas Sellers, Ph.D.
PRINCIPAL INVESTIGATOR: Dawn Grabrick, MPH

CONTRACTING ORGANIZATION: Mayo Foundation
Rochester, Minnesota 55905

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Mayo Foundation
Rochester, Minnesota 55905

e-mail:
grabrick.dawn@mayo.edu

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13. ABSTRACT *(Maximum 200 Words)*

Early age at menarche, nulliparity, late age at first birth, and late age at menopause have been consistently associated with an increased risk of breast cancer. The association of these factors in addition to other reproductive and fertility factors with risk of breast cancer is less well characterized in women with a family history of breast cancer. The scope of this research is to examine the association of reproductive and fertility factors with risk of breast cancer among sisters, daughters, granddaughters, and nieces of 426 breast cancer probands as well as women who married into the 426 families. We found that women who have used oral contraceptives and also have a first-degree relative with breast cancer were at significantly increased risk of breast cancer compared to genetically comparable women who never used oral contraceptives. The association was particularly strong in families with multiple cases of breast and ovarian cancer and for oral contraceptive use before 1975. Further follow-up is needed of younger women who used oral contraceptives after 1975. These findings are very important in light of the published recommendations that women with a hereditary predisposition to breast and ovarian cancer take oral contraceptives to lower risk of ovarian cancer.

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Daron M. Grabrick 10/25/99

PI - Signature Date

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Introduction

Several reproductive factors, including an early age at menarche, nulliparity, late age at first birth, and late age at menopause have been consistently associated with an increased risk of breast cancer. The association of these factors in addition to other reproductive and fertility factors with risk of breast cancer is less well characterized in women with a family history of breast cancer. The scope of this research is to examine the association of reproductive and fertility factors with risk of breast cancer among sisters, daughters, granddaughters, and nieces of 426 breast cancer probands as well as among women who married into the 426 families. Variables to be examined include age at menarche, age at menopause, parity, age at first and last birth, oral contraceptive use, DES exposure, difficulty becoming pregnant, reason for difficulty becoming pregnant, and use of Clomid. The results of this research could have important implications for breast cancer prevention and early detection in women with a family history of breast cancer.

Body

Much progress has been made on the proposed research. Task 1, which involved preparing the data for analyses, has been completed. Consistency checks of the data were performed. Datasets were merged together and appropriate exclusion criteria applied to create the analytic cohort.

Task 2 is to perform the statistical analyses examining the risk of breast cancer associated with the interaction of a family history of breast cancer with reproductive and fertility factors. Because these analyses are being performed in the context of a family study, the first step was to become familiar with statistical methods for analyzing family data. To account for the nonindependence of observations within a family, we are using a robust variance estimate. This is an approximation to the jackknife estimate of variance, which involves repeated sampling of the data, but is computationally faster.

Analyses of oral contraceptive use have been completed, and analyses of other reproductive and fertility factors have recently begun. Our research on oral contraceptive use has yielded important findings for women with a family history of breast cancer. Ever use of oral contraceptives was associated with significantly increased risk of breast cancer among sisters and daughters of breast cancer probands (relative risk=3.3; 95% C.I.: 1.6-6.7), but not among granddaughters and nieces of probands or among marry-ins. Results were essentially unchanged after adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education.

Since granddaughters and nieces may have a closer affected relative than the original proband in the family, analyses of oral contraceptive use were also run with degree of relationship redefined as one's closest affected relative. This resulted in 176 granddaughters and nieces being reclassified into the highest risk category. The results were virtually unchanged.

To study families most likely to be carrying a mutation in BRCA1 or BRCA2, analyses were conducted in high-risk families defined by the number of breast and ovarian cancers among the blood relatives. Among 132 high risk families in which at least 3 blood relatives were diagnosed with breast or ovarian cancer, the interaction of oral contraceptive use with degree of relationship reached even stronger statistical

significance (p=0.006) than in the entire cohort of 426 families. Among sisters and daughters, ever use was associated with a relative risk of 4.6 (95% C.I.: 2.0-10.7). Use of oral contraceptives by granddaughters, nieces, and marry-ins was not associated with significantly increased risk of breast cancer. When the analysis was limited to 35 very high risk families in which at least 5 blood relatives were diagnosed with breast or ovarian cancer, the risk among sisters and daughters was even greater (relative risk=11.4; 95% C.I.: 2.3-56.4).

We questioned whether the elevated risk of breast cancer associated with oral contraceptive use in sisters and daughters of the proband was due to these individuals being more likely to have been exposed to the earlier formulations of oral contraceptives that contained higher doses of estrogen. The amount of estrogen in oral contraceptives has decreased from an initial 150 micrograms to less than 50 micrograms currently, with concurrent decreases in the level of progestogens. While we had collected data on the particular years of oral contraceptive use, we did not ascertain exact formulations or dosages. With the data available, we examined estimated years of exposure to high dose and years of exposure to low dose formulations. Since all oral contraceptives initially marketed after 1975 contain less than 50 micrograms of ethinyl estradiol and 1 mg or less of several progestins, we used this year as the cutpoint. No association was observed between oral contraceptive use after 1975 and risk of breast cancer for any category of family history, although statistical power was limited. However, the risk of breast cancer associated with oral contraceptive use prior to 1975 was elevated among women with a first degree family history of breast cancer (relative risk=3.3; 95% C.I.: 1.5-7.2), but not among women with a second degree family history (relative risk=1.3; 95% C.I.: 0.8-2.0) or among marry-ins (relative risk=1.2; 95% C.I.: 0.8-1.9).

Our results suggest that the use of oral contraceptives in women with a strong family history of breast cancer may further elevate their breast cancer risk. Because the mean age at interview of women with a first degree family history of breast cancer who used oral contraceptives after 1975 was only 43 years, further follow-up is needed to investigate any association between current formulations of oral contraceptives and breast cancer incidence in these high-risk women. Therefore, we conclude that women who have a first degree family history of breast cancer and *any* oral contraceptive exposure may want to be particularly vigilant regarding appropriate breast cancer screening practices.

These findings were presented as a 4-day poster at the 49th Annual Meeting of the American Society of Human Genetics in San Francisco this month. In addition, we are ahead of schedule on task 3: manuscript preparation, scheduled for months 18-24. We recently submitted a manuscript on the oral contraceptive findings to the New England Journal of Medicine.

Key Research Accomplishments

- Women who have used oral contraceptives and have a first degree family history of breast cancer may be at particularly high risk for breast cancer.
- The association between oral contraceptive use and breast cancer in first degree relatives was particularly strong in families with multiple cases of breast and ovarian cancer and for oral contraceptive use prior to 1975.
- The oral contraceptive findings were presented as a poster at the 49th Annual Meeting of the American Society of Human Genetics, and have been submitted for publication to the New England Journal of Medicine.

Reportable Outcomes

Manuscripts

Grabrick DM, Hartmann LC, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM, Olson JE, Couch FJ, Anderson KE, Pankratz S, Sellers TA: Increased risk of breast cancer associated with oral contraceptive use in women with a strong family history of breast cancer. (Submitted: New England Journal of Medicine)

Abstracts

Grabrick DM, Cerhan JR, Couch FJ, Vierkant RA, Therneau TM, Vachon CM, Olson JE, Pankratz VS, Hartmann LC, Sellers TA: Association of oral contraceptives with breast cancer risk in a population-based sample of 426 breast cancer families. The 49th Annual Meeting of the American Society of Human Genetics, October 1999.

Other posters in each topic are scheduled for 2-day (W/T) or 2-day (F/S) display. See p. A-1 for complete listings.

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Association of the C677T polymorphism in the MTHFR gene with breast and/or ovarian cancer risk in Jewish women. *R. Gershoni-Baruch[1,2], E. Dagan[1, 2], D. Israel[3], E. Friedman[3].* 1) Dept Human Genetics, Rambam Medical Ctr, Haifa, Israel; 2) Bruce Rappoport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel; 3) Susanne Levy Gertner Oncogenetics Unit, Chaim Sheba Medical Center, Tel-Aviv, Israel

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5 methyltetrahydrofolate the primary circulatory form of folate and carbon donor for the re-methylation of homocysteine to methionine. A common missense mutation (C677T) in the MTHFR gene is associated with reduced enzyme activity, hyperhomocysteinemia and increased risk for atherosclerosis. Recently, a marginal association of the C677T polymorphism with endometrial and colorectal cancer was observed. To delineate the putative role of the C677T polymorphism in breast/ovarian tumorogenesis we determined the frequency of this polymorphism in 491 Jewish women with either sporadic (n = 355), hereditary (n = 136) breast and/or ovarian cancer who were all previously genotyped for the three predominant Jewish founder mutations in BRCA: 185delAG, 5382insC and 6174delT. Sixty nine asymptomatic BRCA mutation carriers were similarly analyzed. We found that C677T homozygotes were equally distributed among women with either sporadic (71/355; 20%) or hereditary breast/ovarian cancer (43/ 205; 21%); among women diagnosed with breast cancer prior to age 42 (22/122; 18%) and after that age (42/243; 17.3%); and among BRCA mutation carriers either asymptomatic (11/69; 15.9%) or manifesting cancer (32/136; 23.5%). Among women with bilateral breast cancer and those with both breast and ovarian carcinomas the rate of C677T homozygotes (24/72; 33.3%) was significantly higher (p = 0.0026). This observation, namely, that C677T homozygotes are at greater risk of acquiring a second primary tumor, if further corroborated has important clinical implications.

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A large genomic deletion of *hMLH1* in a family with Muir-Torre syndrome. *J.J.P. Gille[1], M.H.P. Strunk[1], R.J. van Schooten[1], L. Jaspars[2], M.H. Vermeer[3], G. Pals[1], F.H. Menko[1].* 1) Dept. of Clinical Genetics and Human Genetics; 2) Dept. of Pathology; 3) Dept. of Dermatology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands.

Muir-Torre syndrome (MTS) is an autosomal dominant condition characterized by sebaceous gland tumors and visceral malignancies. In kindreds diagnosed with HNPCC (hereditary nonpolyposis colorectal cancer) sebaceous gland tumors and other MTS-associated skin tumors have been recognized. HNPCC is often due to germline mutations in one of five DNA-mismatch repair (MMR) genes (*hMSH2, hMLH1, hPMS1, hPMS2*, and *hMSH6*). Among MTS kindreds 14 *hMSH2* and 2 *hMLH* have been reported in the literature. Evidently, MTS and HNPCC are overlapping syndromes.

We studied a family (C149) in which the index patient (II-1) had two primary colorectal cancers at the age of 32 years. His father (I-1) had recurrent skin lesions diagnosed as sebaceous adenomas, sebaceous epitheliomas, keratoacanthomas with sebaceous differentiation and squamous cell carcinoma. At the age of 58 years this latter patient developed colonic cancer. No other close relatives were diagnosed with large bowel cancer or skin tumors. MSI studies of the colonic tumors of both patients revealed the MSI-H (high) phenotype. Germline mutation analysis of *hMLH1* and *hMSH2* by single strand conformation analysis and direct sequencing revealed that I-1 was apparently homozygote for two frequently occurring *hMLH1* polymorphisms located in exon 8 (696AG) and intron 14 (IVS14-19AG), respectively. Surprisingly, II-1 was not a carrier of any of these two polymorphisms, indicating that both patients were in fact hemizygote and carriers of a (partial) deletion of the *hMLH1* gene. Hemizygosity was confirmed by analysis of CA-repeat markers intragenic (D3S1611) and closely linked to *hMLH1* (D3S2623). No transmittance of alleles from I-1 to II-1 was observed. Our results indicate that both affected relatives are carriers of a genomic deletion of *hMLH1* that encompasses at least exons 8-14. The family presented here is the first MTS family with a large genomic deletion of *hMLH1*.

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Mutational analysis of the RET proto-oncogene in 200 French MEN 2 families: a genotype-phenotype correlation. *S. GIRAUD[1], P. PIGNY[2], P. NICCOLI-SIRE[3], P. NIZARD[1], A. MURAT[4], M. BILLAUD[5], G.M. LENOIR[1], GETC[3].* 1) Lab. de Genetique,Hospital E. Herriot,LYON,FRANCE; 2) Hospital Huriez,LILLE; 3) Hospital La Timone,MARSEILLE; 4) Hotel-Dieu,NANTES; 5) CNRS,UMR 5641,LYON.

Germline mutations of the RET proto-oncogene are associated with three inherited related disorders: multiple endocrine neoplasia type 2A (MEN 2A), type 2B (MEN 2B) and familial medullary thyroid carcinoma (FMTC). We have screened exons 8, 10, 11, 13, 14, 15 and 16 of RET in the germline DNA of 200 MEN 2 families. RET mutations have been identified in 99% of MEN 2A (101/102), 100% of MEN 2B patients (27/27). Mutations of RET were found in 91% of FMTC families (66/72) but in all FMTC families with at least three cases of MTC.The majority of MEN2A mutations identified in our series were missense changes located in the region coding for the extracellular cysteine-rich domain of RET: 86% of the mutations affected codon 634 in exon 11 and 10% involved either codons 609, 611, 618 or 620 in exon 10. Also, two single nucleotide substitutions were found in exons 13 and 14 (Y791F and V804M) in two MEN 2A cases. A unique mutation in exon 16 (M918T) within the RET tyrosine kinase has been identified in all cases. With regard to FMTC, mutations in exons 10 et 11 were found in 54%; of the cases. However, as previously described, the distribution of mutations was dissimilar to MEN 2A since cysteine codons of exons 10 and 11 were affected in 39% and 15%, respectively. Furthermore, a new RET mutation that consists in a nine base pair duplication in exon 8 which creates an additional cysteine codon was characterized in one FMTC kindred. Finally, point mutations at codons that specify residues within the tyrosine kinase domain were found in 35% of the cases: 8% at codon 768 or 790 in exon 13; 20% at codon 804 in exon 14 and 7% at codon 891 in exon 15. Notably, carriers of RET mutations in exons 13 to 15 were characterized by a later age of onset and a variable penetrance of medullar thyroid cancer.Finally, based on the results of our functional analyses we will propose a possible biochemical explanation for the correlation between genotype and phenotype.

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Renal Neoplasms in a Familial Multisystem Syndrome with Fibrofolliculomas as a Cutaneous Marker. *G.M. Glenn[1], M.M. Walther[1], J.R. Toro[1], S. Hewitt[1], P. Duray[1], P.L. Choyke[2], G. Weirich[3], M. Turner[1], W.M. Linehan[1], B. Zbar[3].* 1) Genetic Epidemiology Branch, Urologic Oncology Branch, Dermatology Branch, and Laboratory of Pathology, National Cancer Institute, Bethesda, MD; 2) Diagnostic Radiology Department, National Institutes of Health, Bethesda, MD; 3) Laboratory of Immunobiology, Frederick Cancer Research and Development Center, Frederick, MD.

In our studies of familial kidney neoplasms, we recognized a subset of families with renal tumors who were also affected by lung cysts, pneumothorax, and multiple cutaneous papules. In some family members, skin examinations, biopsies and dermatopathologic diagnoses were consistent with Birt-Hogg-Dube syndrome (BHD), a dominantly inherited predisposition to developing fibrofolliculomas, trichodiscomas, and acrochordons, but previously not known to be associated with internal neoplasms. We found renal neoplasms and BHD segregated together in an autosomal dominant pattern. To identify internal tumors, we performed CT scans of abdomen and pelvis with contrast, high resolution chest CTs, renal sonograms, and now have added colonoscopies to improve ascertainment of cases in families for linkage analysis. With referrals from dermatologists nationwide and abroad, we are studying 23 families with 79 individuals affected with BHD, of which 20 have renal epithelial neoplasms, 19 have spontaneous pneumothorax histories, and 12 have had colon polyps and/or colon carcinoma, and a colon tubulovillus adenoma has been seen. Distribution of renal tumor (RT) number in individuals from BHD families is: 1 RT in each of 6 individuals; 2-3 RTs in 4 individuals; and greater than 2-3 RTs in 10 individuals. Renal histopathologies included: Renal oncocytoma in 10 patients; papillary renal carcinoma in 4 patients; clear cell renal carcinoma in 4 patients; and chromophobe renal carcinoma in 2 patients. It is important to recognize the risk for benign and malignant internal tumors, and pneumothorax in individuals when there is a dermatologic diagnosis of BHD. The number and size of families we are studying should allow demonstration of the phenotypic spectrum and identification of the genetic basis of this genodermatosis associated multisystem and neoplastic syndrome.

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Association of oral contraceptives with breast cancer risk in a population-based sample of 426 breast cancer families. *D.M. Grabrick, J.R. Cerhan, F.J. Couch, R.A. Vierkant, T.M. Themeau, C.M. Vachon, J.E. Olson, V.S. Pankratz, L.C. Hartmann, T.A. Sellers.* Mayo Clinic, Rochester, MN.

Oral contraceptives (OCs) are weakly associated with an increased risk of breast cancer (BC) in the general population, but some data suggest a higher risk among BRCA1 and BRCA2 mutation carriers. This is clinically important as women in breast-ovarian cancer families may consider OC use to reduce their ovarian cancer risk. We analyzed data from the Minnesota Breast Cancer Family Study, a historical cohort study of relatives of 426 BC cases identified between 1944 and 1952, and followed through 1996. Ninety-eight percent of eligible families were recruited, and 93% of members participated. OC use and cancer incidence in sisters, daughters, granddaughters, nieces, and marry-ins were determined through telephone interviews. Through 1996, a total of 239 incident BCs were identified in the cohort of 6,150 women at risk. The lifetime prevalence of ever having used OCs was 51% overall and was similar for blood relatives and marry-ins (p=0.99). We used proportional hazards regression, accounting for birth cohort and correlated family data, to model the association between a time-dependent definition of OC use and age at onset of BC. The association of OC use with BC was examined within strata defined by degree of relationship to the proband, with never users as the reference category within each stratum. Among sisters and daughters, women who used OCs for 1 to 4 years were at 4.2-fold greater risk (95% C.I.: 2.1-8.6); for duration of use greater than 4 years the risk estimate was 2.2 (95% C.I.: 0.8-6.4). The corresponding risk estimates for granddaughters and nieces were 1.3 and 1.2, and for marry-ins 1.1 and 1.3, all nonsignificant. When analyses were repeated among the subset of families with 3+ breast or ovarian cancers, risks associated with OC use were further elevated among first-degree relatives: 5.5 (2.4-12.5) and 3.3 (1.0-11.0) for 1 to 4 and greater than 4 years, respectively. These data suggest that use of oral contraceptives may significantly increase risk of breast cancer among women with a family history of breast cancer, especially those with a strong family history.

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Constitutional chromosomal instability and predisposition to childhood solid tumors; a new syndrome? *B. Hirsch[1], S. Berry[1], B. Bostrom[1,2], S. Sencer[2].* 1) Univ Minnesota Medical School, Minneapolis, MN; 2) Children's Hospitals and Clinics, Minneapolis,MN.

The association between chromosomal instability (CI) and predisposition to malignancy is well documented in a number of genetic disorders. However, there are currently only a few well defined syndromes in which CI data are integrated into diagnostic testing or therapy planning.

We here report four children, from three unrelated families, who may represent a novel genetic syndrome. Clinical findings include IUGR, microcephaly, skin pigmentation anomalies, and/or anal abnormalities. Three children (CIA1, CIB1,CIC2)developed Wilms tumors within the first 2 yrs.of life,and one child (CIC1, the older sibling of CIC2),a high grade astrocytoma at 2.5 yrs. After surgical resection, chemotherapy was given to all but CIC2. Two children succumbed to therapy-associated AML within one yr., one died from therapy associated pancytopenia and sepsis. CIC2, who was not given chemotherapy because of concern for hypersensitivity, is alive 5 months post surgery. The three who succumbed all received topoisomerase II inhibitors.

G-banded metaphase analysis from blood lymphocytes and/or skin fibroblasts revealed markedly elevated rates of chromosomal breaks and rearrangements, 50 fold or greater relative to laboratory norms. No recurring abnormality or breakpoint was detected between children; however "clonal" rearrangements were found within individual studies. The pattern and rates of CI were not characteristic of a known disorder. SCE rates were normal, i.e. not indicative of Bloom syndrome.

The etiology of this syndrome is unknown. No mutation of the NF1 gene in patient CIAC2 was found. Although there was no prior significant cancer history in these families, analyses of mismatch repair genes are planned. Constitutional CI is clearly a hallmark of this disorder. Recently, a sibling to CIB1 was born with IUGR,microcephaly and displaced anus. Cytogenetic analysis revealed marked CI, as a result of which this patient is being carefully monitored for tumor development.

Increased risk of breast cancer associated with oral contraceptive use in women with a strong family history of breast cancer

Dawn M. Grabrick, M.P.H., Lynn C. Hartmann, M.D., James R. Cerhan, M.D., Ph.D., Robert A. Vierkant, M.A.S., Terry M. Therneau, Ph.D., Celine M. Vachon, Ph.D., M.P.H., Janet E. Olson, Ph.D., M.P.H., Fergus J. Couch, Ph.D., Kristin E. Anderson, Ph.D., M.P.H., Shane Pankratz, Ph.D., Thomas A. Sellers, Ph.D., M.P.H.

From the Departments of Health Sciences Research (D.M.G., J.R.C., R.A.V., T.M.T., C.M.V., J.E.O., S.P., T.A.S.), Medical Oncology (L.C.H.), and Laboratory Medicine and Pathology, Biochemistry, and Molecular Biology (F.J.C.), Mayo Clinic and Mayo Clinic Cancer Center, Rochester, Minn.; and the Division of Epidemiology, University of Minnesota School of Public Health, and University of Minnesota Cancer Center, Minneapolis, Minn (K.E.A.). Address reprint requests to Dr. Sellers at the Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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Running Head: Oral contraceptive use in breast cancer families

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Abstract

Background Oral contraceptive use is weakly associated with breast cancer risk in the general population. The association among women with a familial predisposition to breast cancer is less clear.

Methods We conducted a historical cohort study of 426 breast cancer families ascertained between 1944 and 1952. Data on oral contraceptive use and incidence of breast cancer through 1996 were obtained from 394 sisters and daughters of the probands, 3,002 granddaughters and nieces, and 2,754 women who married into the families.

Results After accounting for age and birth cohort, ever use of oral contraceptives was associated with significantly increased risk of breast cancer among sisters and daughters of the proband (relative risk=3.3; 95% C.I.: 1.6-6.7), but not among granddaughters and nieces of the proband or among marry-ins. Results were essentially unchanged after adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education. Risks associated with oral contraceptive use in 35 families with 5 or more breast/ovarian cancers were further increased among sisters and daughters (RR=11.4; 95% C.I.: 2.3-56.4); a small effect was observed among granddaughters and nieces (RR=1.4; 95% C.I.: 0.6-3.3). The elevated risk

among women with a first degree family history of breast cancer was most evident for oral contraceptive use prior to 1975, formulations likely to contain higher doses of estrogen (≥50 micrograms).

Conclusions Women who have ever used earlier formulations of oral contraceptives and also have a first degree relative with breast cancer may be at particularly high risk for breast cancer. Further follow-up of these women with a strong family history who used more recent low-estrogen formulations of oral contraceptives is needed to determine how women with a familial predisposition to breast cancer should be advised regarding oral contraceptive use today.

Key Words: Breast neoplasms; contraceptives, oral; epidemiology; risk factors; genetics

Background

In general population samples, oral contraceptives (OCs) have been observed to be weakly associated with risk of breast cancer up to ten years after a woman discontinues use.[1] However, much less is known regarding this association among women with a familial predisposition to breast cancer, with some studies showing a higher risk among women with a family history[2-7], while others have found little or no such evidence.[8-18] Observational studies have demonstrated a reduction in risk of ovarian cancer with oral contraceptive use. As a result, women from high-risk breast-ovarian cancer families are often counseled to take OCs to reduce their ovarian cancer risk.[19, 20] However, a small study of Ashkenazi Jewish women with breast cancer suggests that oral contraceptive use may more greatly increase the risk of breast cancer in carriers of BRCA1 or BRCA2 mutations than in noncarriers.[21]

Since a family history of breast cancer may not only reflect shared genes but also shared exposures, a family study that incorporates carefully ascertained risk factor data is a robust approach to examine the potential interaction of OC use with family history. We evaluated the association between oral contraceptive use and breast cancer risk by family history of the disease in a large historical cohort of Minnesota breast cancer families. In addition, we have data on

total duration and dates of oral contraceptive use, including the ages of exposure, and on potential confounding factors. To our knowledge, this is the first study to examine this interaction in the context of a multigenerational family study, where detailed data on three generations of women are available.

Methods

Study Population

Details of the study design and methods have been published.[22] Briefly, this study originated from a case-control family study initiated in 1944 at the Dight Institute for Human Genetics at the University of Minnesota.[23] A consecutive series of 544 women diagnosed with breast cancer were ascertained between 1944 and 1952 to examine the influence of childbearing, breastfeeding, and hereditary susceptibility on the risk of breast cancer.

A follow-up study of the families of these probands was conducted between 1991 and 1996.[22] Of 544 families in the cohort at the start of follow-up in 1952, we excluded 40 families because the proband had prevalent breast cancer (diagnosed before 1940) and 42 families because no or very few relatives were alive at baseline. Of the remaining 462 families, 20 were lost to follow-up, 10 had no living members in the sampling frame, and 6 families refused to

participate. A total of 426 families (92.2% after baseline exclusions) were successfully updated. The current analysis was restricted to adult sisters, daughters, granddaughters, nieces, and marry-ins in these families who participated in a telephone interview.

Data Collection

Data on cancer history and risk factors for breast cancer were collected through a telephone interview. The participation rate for the telephone interview was 93.0%. A sample of 104 breast cancers has been validated, and the accuracy of self-report has been shown to be very high (99%). To increase validity of reports, collection of data on oral contraceptive use was limited to women who were still living and able to complete the telephone interview. Data include ever versus never use of oral contraceptives, age use began, and age use stopped.

Statistical Analyses

Analyses were performed using Cox proportional hazards regression.[24] Exclusions were made for cancers (other than skin) diagnosed before baseline (defined as proband's date of breast cancer diagnosis). Follow-up began at age 18 or age when the proband in the family was diagnosed, whichever was later. Follow-up continued until age at breast cancer diagnosis or age at interview, whichever came first.

Survival was modeled as a function of age, since age is a better predictor of breast cancer risk than is length of follow-up time in this study.[25] Oral contraceptive use was modeled as a time-dependent variable. Only OC exposure occurring prior to breast cancer diagnosis was included. Analyses were stratified by birth cohort to control for potential cohort effects in OC use and breast cancer incidence. In addition, we accounted for the nonindependence of observations within families by using a robust variance estimate.[26]

The overall association of oral contraceptive use with breast cancer risk in the entire cohort was examined first. Subsequent analyses evaluated whether the degree of relationship to the proband modified the effect of OC use on breast cancer risk. Never OC users were defined as the reference group for each category of relationship to the proband.

Since granddaughters and nieces may have a closer affected relative than the original proband in the family, analyses of oral contraceptive use were also run with degree of relationship redefined as one's closest affected relative. This resulted in 176 granddaughters and nieces being reclassified into the highest risk category. The results were essentially unchanged. Therefore, analyses define family history as relationship to the proband unless otherwise specified.

Potential confounding variables were evaluated for each model after allowing for the interaction of relationship to proband with oral contraceptive use. A variable was considered a confounder if its addition changed the hazard ratio for any of the OC by relationship variables by more than 10%. There was no evidence for confounding by the following variables: parity and age at first birth, education, age at menarche, age at menopause, oophorectomy, lifetime alcohol intake, and body mass index. Diabetes, smoking, and fibroid tumors of the uterus, potential contraindications for OC use, were also ruled out as confounders. Polycystic ovaries and endometriosis, possible indications for using OCs, were evaluated as potential confounders, but they also did not influence the results. In addition to evaluating potential confounders on an individual basis, we fit multivariate models with simultaneous adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education. Since the risk ratios generally changed by less than 10% in these multivariate models, we have presented the most parsimonious models, unadjusted for these variables but accounting for age, birth cohort, and nonindependence of observations within a family. Any meaningful changes upon adjustment are presented in the results. Data analyses were performed using the SAS (SAS Institute, Inc., Cary, NC) and Splus (Mathsoft, Inc., Seattle, WA) software systems.

Results

Description of the Cohort

The age at diagnosis of breast cancer among the original probands showed wide variation, with a range of 21 to 88 years. This is reflected in the birth cohorts of the relatives (Table 1). The study cohort consists of 3,396 blood relatives and 2,754 marry-ins (6,150 total). Breast cancer occurred in 153 of the blood relatives and 86 of the marry-ins during the follow-up period since 1952. The age at onset of breast cancer ranged from 25 to 83. The mean length of follow-up was 31.6 years.

In the study cohort, the lifetime prevalence of ever having used OCs was 51% overall and was similar for blood relatives and marry-ins (p=0.99); 6.5% of ever users reported current use of oral contraceptives. Among women who ever took OCs, the average length of use was 7.0 years (range 0.5 to 37.5 years).

Table 2 describes oral contraceptive use by relationship to the proband. Sisters and daughters of the proband were less likely to have used oral contraceptives than were nieces, granddaughters, and marry-ins, and were more likely to start and end OC use at later ages. The

duration of use did not markedly differ by relationship, but was slightly lower among sisters and daughters.

Table 3 shows the distribution of breast cancer risk factors by oral contraceptive use. Women who had ever used oral contraceptives were much more likely to be premenopausal at the time of interview than women who had never used OCs (52% vs. 9%). Oophorectomy was slightly less common among OC users, while smoking was more common among users than nonusers. OC users also tended to have a higher level of education.

Association of Oral Contraceptives with Breast Cancer

Among the entire cohort, ever use of oral contraceptives was associated with a relative risk of 1.4 (95% C.I.: 1.0-2.0) for breast cancer. Risk did not differ by duration of use (defined by the median split). The relative risk (RR) associated with 1 to 4 years of OC use versus never use was 1.5 (95% C.I.: 1.0-2.3), while greater than 4 years of use conferred a RR of 1.3 (95% C.I.: 0.9-1.9).

Modification of the OC-Breast Cancer Association by Relationship to Breast Cancer Probands

To determine if the apparent risk associated with OC use was modified by genetic background, analyses were performed within strata defined by relationship to the proband (Table

4). Never users served as the reference group within each stratum. In the 426 families, sisters and daughters who ever used OCs were at significantly increased risk of breast cancer compared with sisters and daughters who never used OCs (RR=3.3; 95% C.I.: 1.6-6.7). The risk of breast cancer associated with OC use was not elevated among granddaughters, nieces, or marry-ins. The test for interaction between degree of relationship to the proband and OC use was statistically significant (p=0.03). Although based on a relatively small number of cases, risk ratios did not significantly differ for any relationship category by duration of OC use (1-4 years versus >4 years), by age at first use (≤25 versus >25 years old), by time since first use (≤10 versus >10 years), or by time since last use (≤10 versus >10 years; data not shown).

Analyses in High-Risk Families

To study families most likely to be carrying a mutation in BRCA1 or BRCA2, analyses were conducted in high-risk families defined by the number of breast and ovarian cancers among the blood relatives (Table 4). Among 132 high risk families in which at least 3 blood relatives were diagnosed with breast or ovarian cancer, the interaction of OC use with degree of relationship reached even stronger statistical significance (p=0.006) than in the entire cohort of 426 families. Among sisters and daughters, ever use was associated with a relative risk of 4.6

(95% C.I.: 2.0-10.7). Use of OCs by granddaughters, nieces and marry-ins was not associated with significantly increased risk of breast cancer. When the analysis was limited to 35 very high risk families in which at least 5 blood relatives were diagnosed with breast or ovarian cancer, the risk among sisters and daughters was even greater (RR=11.4; 95% C.I.: 2.3-56.4).

Since defining high risk families on the basis of the number of cancers does not take into account family size, we also calculated standardized incidence ratios. This was done by applying Iowa's 1973-1977 age-specific incidence rates for breast and ovarian cancer in Caucasian women to the age structure of the at-risk women. A family was defined as high risk for this analysis if at least one more breast or ovarian cancer was observed than was expected based on population incidence rates. This resulted in 98 families being classified as high risk. The results were in the same direction as when high risk was based on a simple count of the number of cancers in the family: RR=3.6 (95% C.I.: 1.5-8.7) for sisters and daughters, RR=1.0 (95% C.I.: 0.5-2.0) for granddaughters and nieces and RR=1.1 (95% C.I.: 0.7-1.7) for marry-ins. When the analysis was conducted in 38 families with two excess breast or ovarian cancers, the relative risk of breast cancer among sisters and daughters who used OCs increased to 7.1 (95% C.I.: 2.5-19.7), and the relative risk among granddaughters and nieces increased to 1.7 (95% C.I.: 0.7-

4.3). Adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education decreased the relative risk for sisters and daughters to 5.2 (95% C.I.: 1.9-14.3) and increased the relative risk for granddaughters and nieces to 2.3 (95% C.I.: 0.8-6.2).

Dates of Oral Contraceptive Use

We questioned whether the elevated risk of breast cancer associated with oral contraceptive use in sisters and daughters of the proband was due to these individuals being more likely to have been exposed to the earlier formulations of OCs that contained higher doses of estrogen. The amount of estrogen in oral contraceptives has decreased from an initial 150 micrograms to less than 50 micrograms currently, with concurrent decreases in the level of progestogens. Although we collected data on the particular years of oral contraceptive use, we did not ascertain exact formulations or dosages. With the data available, we examined estimated years of exposure to high dose and years of exposure to low dose formulations. Since all OCs initially marketed after 1975 contain less than 50 micrograms of ethinyl estradiol and 1 mg or less of several progestins [27], we used this year as the cutpoint. Results are presented by closest affected relative to maximize statistical power (Table 5). (Results were unchanged when

analyses were conducted by relationship to the proband.) No association was observed between OC use after 1975 and risk of breast cancer for any category of family history, although statistical power was limited (e.g., only two cases among 60 exposed women with a first degree family history of breast cancer). However, the risk of breast cancer associated with OC use prior to 1975 was elevated among women with a first degree family history of breast cancer (RR=3.3; 95% C.I.: 1.5-7.2), but not among women with a second degree family history (RR=1.3; 95% C.I.: 0.8-2.0) or among marry-ins (RR=1.2; 95% C.I.: 0.8-1.9).

Discussion

Our results suggest that the use of oral contraceptives in women with a strong family history of breast cancer may further elevate their breast cancer risk. Sisters and daughters of the proband who ever used OCs had over a 3-fold increased risk of breast cancer compared to genetically comparable women who never used OCs. The risk was further elevated when analyses were conducted in high-risk families. Upon stratification by oral contraceptive use before or after 1975, the elevated risk of breast cancer was most evident for women with a first degree family history of breast cancer who used oral contraceptives prior to 1975. However, the

mean age at interview for those who used oral contraceptives after 1975 was only 43 years (range 26-67 years).

We expected the risk of breast cancer associated with oral contraceptive use among women with a second degree family history of breast cancer to fall somewhere in-between that for first degree relatives and marry-ins. Although this was not evident in the entire cohort of 426 families, there was some suggestion of an increased risk among second degree relatives when the analyses were conducted in high-risk families and adjustment was made for other breast cancer risk factors. The lack of substantial evidence for an increased risk in the second degree relatives may be due to the younger age of these women. The mean age of the granddaughters at the time of interview was only 45.3 years.

To our knowledge, this study is the first to examine the association of oral contraceptive use with risk of breast cancer within the context of a multigenerational family study. Previously it was recommended that women with mutations in BRCA1 or BRCA2 consider oral contraceptive use to reduce their risk of ovarian cancer.[19] Although our findings are not directly comparable since we did not analyze DNA for these mutations for all cases, the results seen in our highest risk families suggest that women with a genetic predisposition may be at greatly

elevated risk of breast cancer if they use oral contraceptives. Effective prevention against ovarian cancer is certainly desirable given the high mortality associated with this malignancy and the difficulty of early detection. However, breast cancer is a more common occurrence than ovarian cancer in these high-risk families. Additional evidence for women at high risk avoiding OC use comes from a recent study which suggests OCs may more greatly increase the risk of breast cancer in BRCA1 or BRCA2 mutation carriers than in non-carriers, although these results should be viewed with caution given the small sample size.[21]

We found that women who have the highest risk of breast cancer associated with oral contraceptive use are also most likely BRCA1 or BRCA2 mutation carriers. In fact, 5 of the 16 women with a first degree family history of breast cancer who were exposed to oral contraceptives and had breast cancer themselves are in families segregating a mutation in BRCA2 (3 are in families not found to be segregating a mutation in BRCA1 or BRCA2; 8 are in families not yet tested). A mutation has been verified in 3 of these 5 individuals. Of the two remaining individuals, one tested negative for the mutation while the other individual has not been tested. Only two of the 16 individuals had any OC exposure after 1975. Although the risk of breast cancer appears to be greatly increased in the highest risk families, the elevated risk seen

in sisters and daughters of the probands in the entire cohort of 426 families is still of considerable magnitude.

We are not aware of any studies that have examined the risk of breast cancer associated with oral contraceptive use classified according to estrogen dose in women with a family history of breast cancer. Considering the years of ascertainment in most published studies that examined oral contraceptive use and breast cancer risk by a family history of breast cancer, women could have been exposed to either low or high dose formulations or both. It is possible that this heterogeneity of exposure led to some of the inconsistencies observed in previous studies. Several studies, including the Nurses' Health Study [14, 18] and the Cancer and Steroid Hormone Study [11, 15] did not observe increased risks of breast cancer associated with oral contraceptive use among women with a family history of breast cancer. Our findings may have differed because our cohort is enriched for a family history of breast cancer. Other studies that have shown an increased risk of breast cancer associated with OC use include studies focusing on early onset cases with a first degree family history of breast cancer (e.g., UK National Case-Control Study Group[5]) and studies of known BRCA1 or BRCA2 mutation carriers.[21]

In vitro experiments on breast cancer cell lines have shown that wild-type BRCA1 inhibits the transcription activity of the estrogen receptor ER-α.[28] Mutations in BRCA1 may remove this inhibitory effect, thereby increasing estrogen-dependent epithelial proliferation in the breast. This proposed interaction between BRCA1 and the estrogen receptor may contribute to the increased risk associated with oral contraceptive use observed in some of our families.

The Minnesota Breast Cancer Family Study is a unique, well-defined resource for genetic epidemiologic studies. One important advantage of this resource of multigenerational families is that the selection of the original breast cancer probands was essentially population-based. Participation rates have been very high (>93%), with on average only one or two individuals per family lost to follow-up. The length of follow-up for an individual in this analysis of oral contraceptive use and breast cancer risk was extensive, on average over 30 years and as long as 64 years. Recall of oral contraceptive use is expected to be quite accurate for the characteristics we analyzed, namely ever versus never use, total duration of use, and ages of use. Agreement between recalled history and records of prescribing gynecologists for these aspects of oral contraceptive use have been shown to be reasonably good and nondifferential with regard to case/control status.[29]

Several complicating factors must be considered when interpreting the results of this study, however. Trends in oral contraceptive use in the United States have been quite pronounced. Prevalence of OC use has increased markedly over time, especially among younger women. Total duration of use has increased as well. In addition, substantial changes in the type and concentration of the estrogen and progestin components of oral contraceptives have occurred since their introduction in 1960, from 150 micrograms of mestranol to less than 50 micrograms of ethinyl estradiol, and 9.85 milligrams of norethynodrel to 1 milligram or less of several progestins. [27] The rising incidence of breast cancer over the years of follow-up further complicates the analysis. Although we adjusted for quartiles of birth cohort, we were unable to completely control for all temporal trends. Our estimation of low versus high dose formulations of oral contraceptives was based on use before or after 1975 since all formulations of OCs initially marketed after 1975 contain less than 50 micrograms of ethinyl estradiol and 1 milligram or less of several progestins.[27] Therefore, some misclassification of high dose versus low dose exposure likely occurred. Since most instances of misclassification would result in individuals with low dose exposure being classified as having high dose exposure, we consider this to be a conservative approach.

Surrogate data on OC use were not collected due to their potentially low reliability. Therefore, data on OCs are limited to women who were alive and able to complete the telephone interview between 1991 and 1996. If OCs are associated with improved survival after breast cancer, one would expect to see an increased risk of breast cancer associated with OC use in this cohort. While some evidence exists for breast cancers in OC users being earlier stage, it is unknown whether this stems from earlier detection of breast cancer in these women, from the biological effects of the OCs, or a combination of reasons.[1] As evidence against survivor bias, the relative risk of breast cancer associated with OC use among the marry-ins in our cohort is comparable to published estimates in general population samples.[1]

In summary, women with a first degree family history of breast cancer who used oral contraceptives prior to 1975 were at significantly increased risk of breast cancer. We saw no evidence for an increased risk of breast cancer associated with use of oral contraceptives after 1975 in first degree relatives, second degree relatives, or marry-ins. However, only 60 women with a first degree family history of breast cancer used oral contraceptives after 1975 and only 2 of these were diagnosed with breast cancer, so our estimated relative risk is somewhat unstable for this group of younger women. Also, because of the potential for misclassification of

exposure, we are hesitant to draw conclusions regarding the influence of more recent OC formulations on breast cancer risk in women with a first degree family history of breast cancer. Further follow-up is needed to investigate any association between current formulations of oral contraceptives and breast cancer incidence in these high-risk women. In addition, we will be completing BRCA1/2 mutation screening in the high risk families to determine whether these or other genes are responsible for the modifying effect of family history on the association between oral contraceptive use and breast cancer. Women who have a first degree family history of breast cancer and oral contraceptive exposure may want to be particularly vigilant regarding appropriate breast cancer screening practices.

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Table 1. Description of a cohort of 426 families ascertained through probands diagnosed with breast cancer at the University of Minnesota between 1944 and 1952.

	Relationship to Proband					
	Sisters	Daughters	Granddaughters	Nieces	Marry-ins	Total
Birth cohort:						
<1913	30 (41%)	30 (9.3%)	3 (0.2%)	133 (8.4%)	143 (5.2%)	339 (5.5%)
1913-1925	38 (52.8%)	130 (40.4%)	65 (4.6%)	590 (37.5%)	639 (23.2%)	1462 (23.8%)
1926-1941	4 (5.6%)	140 (43.5%)	339 (23.8%)	592 (37.6%)	955 (34.7%)	2030 (33.0%)
≥1942	0 (0%)	22 (6.8%)	1020 (71.5%)	260 (16.5%)	1017 (36.9%)	2319 (37.7%)
Mean age (range), years[a]	79.0 (62-93)	67.6 (36-89)	45.3 (18-84)	65.0 (20-95)	57.5 (21-94)	57.4 (18-95)
Number of breast cancers[b]	6	32	24	91	86	239
Mean age at breast cancer onset (range), years	60.0 (50-73)	56.6 (34-83)	50.4 (25-72)	57.0 (26-81)	57.5 (27-82)	56.5 (25-83)

[a] At time of interview

[b] Diagnosed between 1952 and 1996

Table 2. Characteristics of oral contraceptive use by relationship to proband in a cohort of 426 families.

	Relationship to Proband		
	Sisters, Daughters (n=394)	Nieces, Granddaughters (n=3002)	Marry-ins (n=2754)
Never used	76.9%	45.0%	48.7%
Current users	0%	4.5%	2.6%
Former users	23.1%	50.5%	48.7%
Mean age at first OC use, years (SD)	30.1 (7.1)	23.8 (6.8)	24.5 (6.8)
Mean age at end of OC use, years (SD)[a]	35.6 (7.4)	30.5 (8.1)	30.8 (8.0)
Mean duration of OC use, years (SD)[a]	6.0 (5.8)	7.2 (5.9)	6.8 (5.8)

[a] includes current users

Table 3. Distribution of breast cancer risk factors by oral contraceptive use in a cohort of 426 families, 1991 – 1996.[a]

	Oral Contraceptive Use	
Risk Factors	Ever (n=3156)	Never (n=2994)
Parity/Age at first birth		
Nulliparous	11.4%	12.6%
1-2, ≤20 years	11.3%	6.1%
1-2, >20 years	29.9%	25.7%
3+, ≤20 years	23.0%	19.7%
3+, >20 years	24.5%	35.9%
Mean age at menarche, years (SD)	12.9 (1.5)	13.1 (1.6)
Menopausal Status		
Premenopausal	51.5%	8.6%
Age at menopause <44 years	21.1%	26.2%
Age at menopause 45-50 years	16.6%	35.5%

Age at menopause >50 years	10.8%	29.7%
Oophorectomy	11.0%	18.2%
Smoking History		
Never smoked	45.8%	62.0%
≤20 pack-years	30.3%	17.2%
>20 pack-years	24.0%	20.9%
Education		
< High school graduate	11.7%	29.7%
High school graduate	37.1%	35.4%
Some college	33.4%	25.1%
College graduate	17.8%	9.8%

[a] Distribution of each risk factor differs significantly by OC use, $p<0.001$

Table 4. Association of oral contraceptive use with risk of breast cancer, by relationship to proband, in high risk breast-ovarian cancer families.

		Entire cohort (426 families)[a]			3+ Breast or ovarian cancers (132 families)[b]			5+ Breast or ovarian cancers (35 families)[b]		
Relationship to Proband	Oral contraceptive use	Number of breast cancers	Person-years	RR (95% C.I.)	Number of breast cancers	Person-years	RR (95% C.I.)	Number of breast cancers	Person-years	RR (95% C.I.)
Sisters, Daughters	Ever	13	2533	3.3 (1.6-6.7)	10	733	4.6 (2.0-10.7)	6	326	11.4 (2.3-56.4)
	Never	25	15063	1.0 (ref)	16	5534	1.0 (ref)	3	1991	1.0 (ref)
Nieces, Granddaughters	Ever	37	38178	1.2 (0.8-2.0)	26	14885	1.2 (0.7-2.0)	12	5048	1.4 (0.6-3.3)

	Never	78	67522	1.0 (ref)	61	29985	1.0 (ref)	26	11210	1.0 (ref)
Marry-ins[c]	Ever	26	33930	1.2 (0.8-1.9)	26	33930	1.1 (0.7-1.8)	26	33930	1.1 (0.7-1.8)
	Never	60	67940	1.0 (ref)	60	67940	1.0 (ref)	60	67940	1.0 (ref)

[a] p-interaction<0.05

[b] p-interaction≤0.01

[c] Marry-ins are from all 426 families for all analyses

Table 5. Association of oral contraceptive use before and after 1975 with breast cancer risk, by closest affected relative.[a]

Closest affected relative	Period	OC use	Number of breast cancers	Person-years	RR (95% C.I.)
First degree	≤1975	No	29	20264	1.0 (ref)
		Yes	16	3896	3.3 (1.5-7.2)
	>1975	No	43	23231	1.0 (ref)
		Yes	2	929	0.9 (0.2-4.5)
Second degree	≤1975	No	75	67213	1.0 (ref)
		Yes	33	31923	1.3 (0.8-2.0)
	>1975	No	103	86661	1.0 (ref)
		Yes	5	12475	0.6 (0.2-1.3)
Marry-ins	≤1975	No	60	71302	1.0 (ref)
		Yes	26	30568	1.2 (0.8-1.9)
	>1975	No	80	92143	1.0 (ref)
		Yes	6	9727	1.1 (0.4-2.6)

[a] Women who used oral contraceptives both before and after 1975 contribute person-years to both groups.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

Rec'd 7/23/2001

file

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 11 July 2001

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical report written for Grant DAMD17-98-1-8212. Request the limited distribution statement for Accession Document Number **ADB262292**, be changed to "**Approved for public release; distribution** unlimited." This report should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management