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MALIGNANCIES FOLLOWING IN-SITU CERVICAL CANCER IN HISPANIC AMERICANS AND NON-HISPANIC WHITES

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ABSTRACT

OBJECTIVES: Some risk factors for cervical cancer in situ convey risk for malignancies of the cervix and other sites. We estimate risk of several malignancies following in situ cancer of the cervix for Hispanic Americans and non-Hispanic Whites.

METHODS: Using California Cancer Registry data (1988-1999) we identify 56,020 women with cervical cancer in situ and observe subsequent malignancies in that cohort, with over three million woman-months of followup. We focus on cancers of the reproductive system and cancers related to smoking. Risk estimates are standardized incidence ratios, accounting for age, time at risk, cancer type, and race/ethnicity.

RESULTS: There is elevated risk for invasive cervical cancer (SIR=4.1, 95%CI: 3.5-4.7), which is significantly higher for Hispanics than for non-Hispanic Whites (SIRs = 5.2 and 3.2, respectively, X²(1) = 7.66, p = .006). Excluding cervix, non-Hispanic Whites show elevated risk for a pool of reproductive cancers (SIR=1.8, 95%CI: 1.4-2.4). While both groups show elevated risk for a pool of smoking-related cancers, only non-Hispanic Whites show significant risk specifically for lung cancer (SIR=1.7, 95%CI: 1.4-2.1). Non-Hispanic Whites show elevated risk for ovarian cancer (SIR=1.8, 95%CI: 1.3-2.4). Ovarian cancer following in-situ cervical cancer is disproportionately of borderline histology (G²(1) = 7.43, p=.006).

CONCLUSIONS: These results have implications for public-health planning for women, as well as better understanding of disparities in care or biologic paths to malignancies in women with in-situ cancer of the cervix.
INTRODUCTION

Cervical cancer remains a grave problem throughout the world, with approximately half a million new cases diagnosed each year [1,2]. Among recognized risk factors for malignant cervical cancer are persistent infection by oncogenic strains of human papilloma virus, tobacco use, and cervical cancer in situ (CCIS) [2,3,4,5,6]. This predictive relationship motivates screening for and treatment of pre-malignant cervical abnormalities. The identification of cervical-cancer precursors, the implementation of screening programs, and efforts at public education, coincide with a recently reported decline in incidence of cervical cancer in the United States[7].

Treating cervical dysplastic lesions may do little to resolve underlying viral infections or modify other constitutional or behavioral susceptibilities to malignancy. Our purpose here is to estimate the strength of association between a diagnosis of CCIS and subsequent invasive cancers of the cervix and other cancer sites. We use records of the population-based California Cancer Registry [8,9,10] to estimate risk for cancers following CCIS in a large, diverse, and population-based cohort of women in which CCIS is the first reported neoplasm.

In California, statewide, mandatory cancer reporting began with diagnoses in 1988 and continues through the present day. CCIS is reportable in California if diagnosed from 1988 through 1995, but not thereafter. Using California Cancer Registry data, we conduct a historical-prospective study of malignancies following a diagnosis of CCIS among female residents of California. We focus on the five most prevalent second-cancer types observed in the cohort, plus cancers
of the female genital system and cancers related to smoking. Unexpected findings of elevated risk of ovarian cancer motivate a case-control comparison of the histology of ovarian cancer, with versus without prior CCIS.
MATERIALS AND METHODS

Cancer Data and Variables. Cancer data are from the Regional Use File [11] of the California Cancer Registry, with case ascertainment considered complete for diagnosis years 1988 through 1999 by the California Department of Health Services. The temporal order of tumors within the same patient is given by the variable sequence number [12]. Cancer type is determined by topography and histology codes from the International Classification of Diseases for Oncology, second edition (ICD-O-2) [13], re-coded according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute [14]. In-situ or invasive status is determined by the behavior code from ICD-O-2. The authors have IRB approval to use these data for this study (UCI IRB 95*203).

Determination of Race/Ethnicity. The California Cancer Registry assigns each reported cancer case to one of six mutually exclusive race/ethnic categories: 1) Asian/Pacific Islander, 2) non-Hispanic Black, 3) Hispanic, 4) Native American, 5) non-Hispanic White, or 6) Unknown. Hispanics are not counted in any other group and may be of any race. The assignment is based on the medical record, supplemented by race/ethnic-specific surname lists [15, 16]. Thus determination of race/ethnicity here is consistent with publications of the California Cancer Registry [e.g., 16]. Except for Unknown, these categories are consistent with corresponding population estimates produced by the Demographic Research Unit of the California Department of Finance [17,18,19].
Risk of Second Cancer. Standardized incidence ratios estimate risk for second cancers [20]. For each cancer type evaluated, we estimate an expected number of cases for the cohort by applying each member’s time at risk to corresponding average annual, sex-, race/ethnic-, and type-specific incidence rates for California as a whole (1995-1999) [16], by five-year age group. Time at risk for each woman is defined as age at diagnosis of CCIS through the earliest of: 1) age at diagnosis of the cancer type in question, 2) age at last follow-up, 3) age 84. Age 84 is the upper bound of conveniently available incidence figures by five-year age group. Risk is assumed to be uniform within each five-year age category. For each woman, a cumulative rate is estimated by summing across age-specific incidence rates from age at diagnosis of CCIS through age at the end of risk. Summing these cumulative rates across cohort members yields an estimate of expected number of cases of the cancer in question. This method accounts for variations in age at first diagnosis, time at risk, and race/ethnicity among cohort members. Risk is incremented in whole years, including the year of diagnosis of CCIS.

Case-Control Methods. A matched case-control study is performed to compare the histology of invasive ovarian cases following CCIS (cases) to that of ovarian cases diagnosed as a patient’s first malignancy, without prior CCIS on record (controls). A pool of potential controls is selected such that invasive ovarian cancer is the first or only cancer on record and age at diagnosis is below 85
years old. The pool of potential controls excludes tumor records based solely on autopsy or death certificate. For each case, prospective controls are selected to match on race/ethnicity, differ by no more than one year on estimated year of birth, and such that the control’s age at diagnosis of ovarian cancer is no younger than the age of diagnosis of CCIS in the corresponding case. Nine controls are selected for each case: where available controls exceed nine the selection is at random. Year of birth is not in the data file, but is estimated by subtracting age at first diagnosis from year of that diagnosis.

Computing and Statistics. The estimated SIRs are evaluated against the null-hypothesis value of one via 95-percent, exact Poisson confidence intervals [20,21]. Differences between SIRs are evaluated with an approximate chi-square statistic [22]. Likelihood-ratio chi square [23] is used to evaluate differences in histologic distribution between cases and controls. The procedures and analyses are accomplished with SAS/STAT® software [24] and DEC FORTRAN programming [25].
RESULTS

Study Cohort. We identify 56020 women diagnosed from 1988 through 1995 with CCIS as the first, or only, reportable cancer, meeting the inclusion criteria given above. Of these, 52% are non-Hispanic White (n=29133) and 26% are Hispanic (n=14561). Each of the other groups comprise less than 10% of the cohort (non-Hispanic Black n=3493; Asian/Pacific Islanders n=3052; Other n=57), and about 10% are of Unknown race/ethnicity (n=5724). We focus on Hispanics and non-Hispanic Whites. Median age at diagnosis of CCIS is 32 overall, and for both Hispanics and non-Hispanic Whites. Median months of observation is 60 for the entire cohort. Given the cutoff age of 84, the number of months between diagnoses of CCIS and the first, subsequent malignant tumor ranges from 0 through 141 (median: 41 months). These data yield 3,047,808 woman-months of followup for the CCIS cohort.

Second Tumor Information. Malignant tumors diagnosed after CCIS are found for 1120 cohort members, including eight cases of bladder cancer in-situ. (We follow convention in including bladder in situ with invasive disease [16]). The 1120 cases distribute across 37 cancer types. The five most prevalent types are breast (n=277), cervix (n=168), lung (n=116), colo/rectal (n=72), and ovary (n=60), which together account for 62% (n=693) of the 1120 cases. We confine our analyses to these more prevalent sites, as well as sites of the female genital system and sites related to smoking. Cancers of the breast and colo/rectum account for 31% of the second tumors in the cohort, across all race/ethnicities.
However, as expected, the SIRs for neither of these cancers is statistically significant (breast SIR=0.9, 95%CI 0.8-1.0; colo/rectal SIR=1.0, 95%CI 0.8-1.3). The SIRs for cancers of the cervix, lung, and ovary are significantly elevated, and given in Table 1.

Table 1 shows estimated SIRs and corresponding 95% confidence intervals overall, and for Hispanics and non-Hispanic Whites separately. The SIRs are significantly elevated for cancers of the cervix, lung, and ovary in the entire cohort and in non-Hispanic Whites. Hispanics show only an elevated risk for cervical cancer. The SIR for cervical cancer in Hispanics is statistically higher than that for Whites (5.23/3.22 = 1.62, X²(1) = 7.66, p =.006).

Table 2 shows SIRs for sites of the female genital system pooled together, with and without cervical cancer, and a pool of smoking-related cancers, with and without lung cancer. All SIRs in the table are significantly elevated, excepting that for the female genital system, excluding cervix, among Hispanics.

RESULTS OF THE CASE-CONTROL STUDY
The bulk of the 60 ovarian tumors observed in the cohort are classified as epithelial (n=34) or borderline (n=25), with one sex-cord case. Consequently we dichotomized histology as \textit{borderline} versus \textit{epithelial and other}. As shown in Table 1, non-Hispanic Whites account for the bulk (72%) of the observed ovarian
cases. Thus we present results on histology of ovarian cancer for all race/ethnicity and non-Hispanic Whites.

Table 3 shows the number and percent of invasive, ovarian cancers classified as borderline histology among cases and controls both across race/ethnicity and for non-Hispanic Whites alone. As may be seen, the proportion of tumors classified as borderline is substantially greater in cases than in controls (all race/ethnicity: $G^2 = 7.4$, $p = 0.007$; non-Hispanic Whites: $G^2 = 5.0$, $p = .03$). To guard against an unrepresentative control group, we took advantage of the large number of prospective controls and repeated the process of control selection and analysis, independently, 14 times. Each repetition yields the same pattern of results (all race/ethnicity, smallest $G^2=5.5$, $p = .02$; non-Hispanic Whites, smallest $G^2=4.0$, $p = .05$).
DISCUSSION

In a diverse, population-based cohort of over 56000 California women with a history of CCIS we observe over four times the expected number of subsequent malignant cervical cancers, relative to the general population of women in California. The risk is significantly higher for Hispanics (SIR=5.23) than for non-Hispanic Whites (SIR=3.22). Non-Hispanic Whites show elevated risk for a pool of female genital malignancies, excluding cervix and ovary, while Hispanics do not. Both racial/ethnic groups show elevated risk for smoking-related cancers, including or omitting lung cancer. Non-Hispanic Whites show elevated risk specifically for lung cancer, and ovarian cancer. Ovarian cancer following CCIS is disproportionately of borderline histology, compared to ovarian cancers that are the first or only record in the cancer registry. While this registry-based study has limitations, the results have implications for further research on cancer etiology and for medical surveillance of CCIS patients.

Because of common risk factors, we expect elevated risk for invasive cervical cancer in the CCIS cohort. However, to our knowledge, this is the largest, population-based study to quantify this risk. Certainly, treatment of dysplastic lesions would not necessarily clear HPV or other infections, or alter smoking or other possible risk factors. Relative to the majority of CCIS patients, those who develop invasive disease may be constitutionally more susceptible, may have more risk factors, may have particular strains or viral loads of HPV [26] or other agents, may have less access to medical care, may receive poorer follow-up surveillance, or be subject to combinations of factors.
The SIRs estimated for Hispanics and non-Hispanic Whites are relative to their respective race/ethnic groups. It is well known from race/ethnic-specific incidence rates that Hispanics have a higher risk for cervical cancer than Whites [27]. Our race/ethnic-specific SIRs account for differences in baseline risk because the expected numbers of cases are race/ethnic specific. Our results show CCIS has a higher positive predictive value for subsequent cervical malignancies in Hispanics than in non-Hispanic Whites, while still a significant predictor for Whites. Explanations for this disparity are speculative, but may include differences in prevalence and spectrum of HPV strains or viral loads between or among populations [26]. Such differences might explain why Hispanics in the CCIS cohort do not show elevation in risk for the pool of female-genital cancers, excluding cervix (Table 2). Of course, differences in access to health care, or quality of care, may explain these results, at least in part. However, the results highlight the importance of risk-reduction counseling and gynecologic surveillance for the Hispanic community of California, and perhaps elsewhere.

Only non-Hispanic White members of the cohort show an elevation in lung-cancer risk. This finding seems consistent with reports that, in California, the prevalence of smoking among non-Hispanic White women is roughly twice that of Hispanic women [28]. However, both Hispanic and non-Hispanic Whites show an elevation in the pool of smoking-related cancers (Table 2). Perhaps Hispanic women in the CCIS cohort are more likely to smoke than Hispanic women in the general population. However, that notion seems to imply elevated
risk for lung cancer among Hispanics in the CCIS cohort: a result we did not find. Passive smoking may be a factor here, as may interactions between HPV distributions and smoking.

Our finding of elevated risk for ovarian cancer following CCIS seems to have no precedent in the literature. Certainly, ovarian cancers may be detected in the course of aggressive treatment of the CCIS. Insofar as aggressive treatment or followup is more likely for non-Hispanic Whites than for Hispanics, the elevated risk for ovarian cancers observed among the non-Hispanic Whites could result from a surveillance bias. While the data set has no information on treatment, differences in the time between diagnoses of CCIS and ovarian cancer seem consistent with a surveillance-bias explanation. Over all race/ethnicities, about 28% (17/60) of the ovarian cases are diagnosed within three months of the CCIS. The corresponding figure is about 35% (15/43) in non-Hispanic Whites, and about 12% (2/17) among Hispanics (Fisher’s Exact Test: p < 0.07). Thus differences in medical care across race/ethnic groups may explain the observed elevation of risk for ovarian cancer subsequent to CCIS, at least in part. However, it is difficult to see how surveillance bias accounts for the histology of ovarian cancers following CCIS. We show that about 40% of such cases are borderline tumors of low malignant potential (Table 3), which is twice the prevalence in our comparison group(s) and higher than published estimates (10-20%) [29,30]. To be sure, this histologic finding is a statistical observation, but one that may call for a biologic investigation.
Strengths of this study include a large CCIS cohort with population-based accrual. Limitations of this study include the completeness of CCIS reporting and limitations of registries to track and link patients. Because CCIS is an ambiguous diagnosis it is likely that some fraction of CCIS cases were never reported, despite the legal mandate to do so in California. Thus our cohort, large as it is, is a subset of California women diagnosed with in-situ cancer of the cervix between 1988 and 1995. Subsequent malignancies in some cohort members may go unrecognized for any number of reasons, from moving out of state through adoption of a different identity. Within any sizable registry, no doubt the processes of correctly identifying individual patients, and tumors within patients, is not perfect. But, the net result seems likely to be underestimates of the number of subsequent malignancies and overestimates of the expected numbers of cases for the study cohort. Thus, we suspect our SIR estimates have a net bias toward the null hypotheses.

While CCIS, per se, has generally a good prognosis, our results reinforce the need for medical surveillance of and risk-reduction programs for CCIS patients. These needs may be greater in Hispanic and perhaps other minority communities. Until, if ever, we can better predict which CCIS patients are susceptible to subsequent malignancies, the CCIS diagnosis is an opportunity for risk-reduction counseling and a justification for medical monitoring and screening for all women. Data such as these may contribute significantly to future public-health planning for women, as well as better understanding of disparities in heath care and biologic paths to malignancies.
Acknowledgements

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ARTICLE PRECIS

Cervical cancer in situ predicts subsequent malignancies more strongly in Hispanics than Whites. Ovarian cancers following cervical cancer in situ are disproportionately of borderline histology.
Table 1
Estimated Standardized Incidence Ratios for Selected Invasive Cancers following In-Situ Cervical Cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Full Cohort</th>
<th>Hispanic</th>
<th>non-Hispanic White</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Observed</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>Expected</td>
<td></td>
<td>SIR(95%CI)</td>
</tr>
<tr>
<td>Cervix</td>
<td>168</td>
<td>41.4</td>
<td>4.1 (3.5-4.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>116</td>
<td>83.0</td>
<td>1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>Ovary</td>
<td>60</td>
<td>40.9</td>
<td>1.5 (1.1-1.9)</td>
</tr>
</tbody>
</table>

Fractions are rounded to tenths.
Table 2
Estimated Standardized Incidence Ratios for Pooled Sites of the Female Genital System* and Smoking-Related Sites+ following In-Situ Cervical Cancer

<table>
<thead>
<tr>
<th></th>
<th>Full Cohort</th>
<th>Hispanic</th>
<th>Non-Hispanic White</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Cases</td>
<td>Cases</td>
</tr>
<tr>
<td>Observed</td>
<td>Expected</td>
<td>SIR (95%CI)</td>
<td>Expected</td>
</tr>
<tr>
<td>257</td>
<td>94.7</td>
<td>2.7 (2.4-3.1)</td>
<td>93</td>
</tr>
<tr>
<td>*Female genital system including cervix but excluding ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>53.3</td>
<td>1.7 (1.3-2.0)</td>
<td>14</td>
</tr>
<tr>
<td>+Smoking related cancers including lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>183</td>
<td>129.5</td>
<td>1.4 (1.2-1.6)</td>
<td>24</td>
</tr>
<tr>
<td>+Smoking related cancers excluding lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>46.5</td>
<td>1.4 (1.1-1.8)</td>
<td>14</td>
</tr>
</tbody>
</table>

*Female genital system includes Uterus, Vagina, Vulva, with or without Cervix

+Smoking-related cancers include Bladder, Buccal Cavity and Pharynx, Esophagus, Larynx, Pancreas, with or without Lung, but excluding Cervix

Fractions are rounded to tenths.
Table 3

Number and Percent of Invasive Ovarian Cancers Classified as Borderline* in Cases+ and Controls+

<table>
<thead>
<tr>
<th>Histologic Classification</th>
<th>Full Cohort</th>
<th></th>
<th>Non-Hispanic Whites</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Number and Column %</td>
<td>Number and Column %</td>
<td>Number and Column %</td>
<td>Number and Column %</td>
</tr>
<tr>
<td>Borderline</td>
<td>25 (41.7%)</td>
<td>133 (24.6%)</td>
<td>17 (39.5%)</td>
<td>90 (23.3%)</td>
</tr>
<tr>
<td>Epithelial and Other</td>
<td>35 (58.3%)</td>
<td>407 (75.4%)</td>
<td>26 (60.5%)</td>
<td>297 (76.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (100%)</td>
<td>540 (100%)</td>
<td>43 (100%)</td>
<td>387 (100%)</td>
</tr>
</tbody>
</table>

* Borderline denotes ICD-O-2 (13) codes of: 8442, 8451, 8462, 8472, or 8473.

+ Cases: ovarian cancer follows in-situ cervical cancer, Controls: ovarian cancer is the first reportable neoplasm

Fractions are rounded to tenths.