A Multi-level Model to Understand Cervical Cancer Disparities in Appalachia

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ABSTRACT

The Appalachian region experiences higher incidence and mortality due to cervical cancer compared with other regions of the United States. The goal of the Ohio State University Center for Population Health and Health Disparities (CPHHD), called the Community Awareness Resources and Education (CARE) project, was to understand reasons for this disparity. The first wave (2003–2008) of funding included three projects focusing on the known risk factors for cervical cancer, lack of screening, smoking, and infection with human papillomavirus (HPV). On the basis of the results of these projects, the second wave (2011–2017) included four projects, designed to address a multi-level model of factors contributing to cervical disparities in Appalachia. The results of these projects were then used to refine a multi-level model that explains cervical cancer disparities in Appalachia. Future funded projects will take these multi-level explanations for cervical disparities and focus on implementation science strategies to reduce the burden of cervical cancer morbidity and mortality in Appalachia.

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Despite declining incidence and mortality associated with cervical cancer in recent decades, certain populations are known to suffer disproportionately from this disease compared with national averages, including women in the Appalachian region (1). Appalachia is a 420-county region in the United States that extends from New York down through to northern Mississippi. Around 8% of the total U.S. population resides in the Appalachian region. Appalachia is less racially diverse than the rest of the United States, as non-Whites make up 18.2% of those living in Appalachia, compared with 38.7% of the U.S. population (2). Around 42% of the Appalachian region is considered as rural, compared with only 20% of the U.S. population (3). Overall, Appalachia is characterized by rural typography and geographic isolation, high rates of poverty, low household incomes, and low educational attainment compared with the rest of the United States (4).

Overall, many factors may contribute to the observed cervical cancer disparities in Appalachia (4), lack of healthcare facilities and providers in the region (5), poor health behaviors (6), and poor communication with healthcare providers (7). Socioeconomic factors such as low income and education, as well as poverty, (4) contribute to this observed cervical cancer disparity in the region. To address reasons for, and potential solutions to the observed disparity in cervical cancer incidence and mortality in the Ohio Appalachian region, Ohio State's CPHHD, called the CARE study, was funded by the NIH (P50 CA105632). The first wave of funding (2003–2008) focused on understanding and intervening on three major factors which may explain cervical cancer disparities in Appalachia—lack of Pap testing, smoking, and HPV infection (8–10). As part of the CPHHD initiative, investigators from all funded sites developed a multi-level model to understand disparities (**Fig. 1**; ref. 11). In the second round of funding (2011–2017), CARE investigators built upon the results of the first round and using the CPHHD multi-level model of health disparities, conducted four projects to understand cervical cancer health disparities at multiple levels, from the biological level (downstream factors) to social conditions and policies (upstream factors; ref. 11). An overall goal was to customize the CPHHD model to specifically describe the multi-level cervical cancer disparities in Appalachia using the results from these four projects. Below, we briefly discuss the objectives and results of each CARE Project (CARE 1 projects 1–3 and CARE 2 projects 1–4) followed by the multi-level model constructed from CARE 2 project results. Future directions based on this model are discussed.

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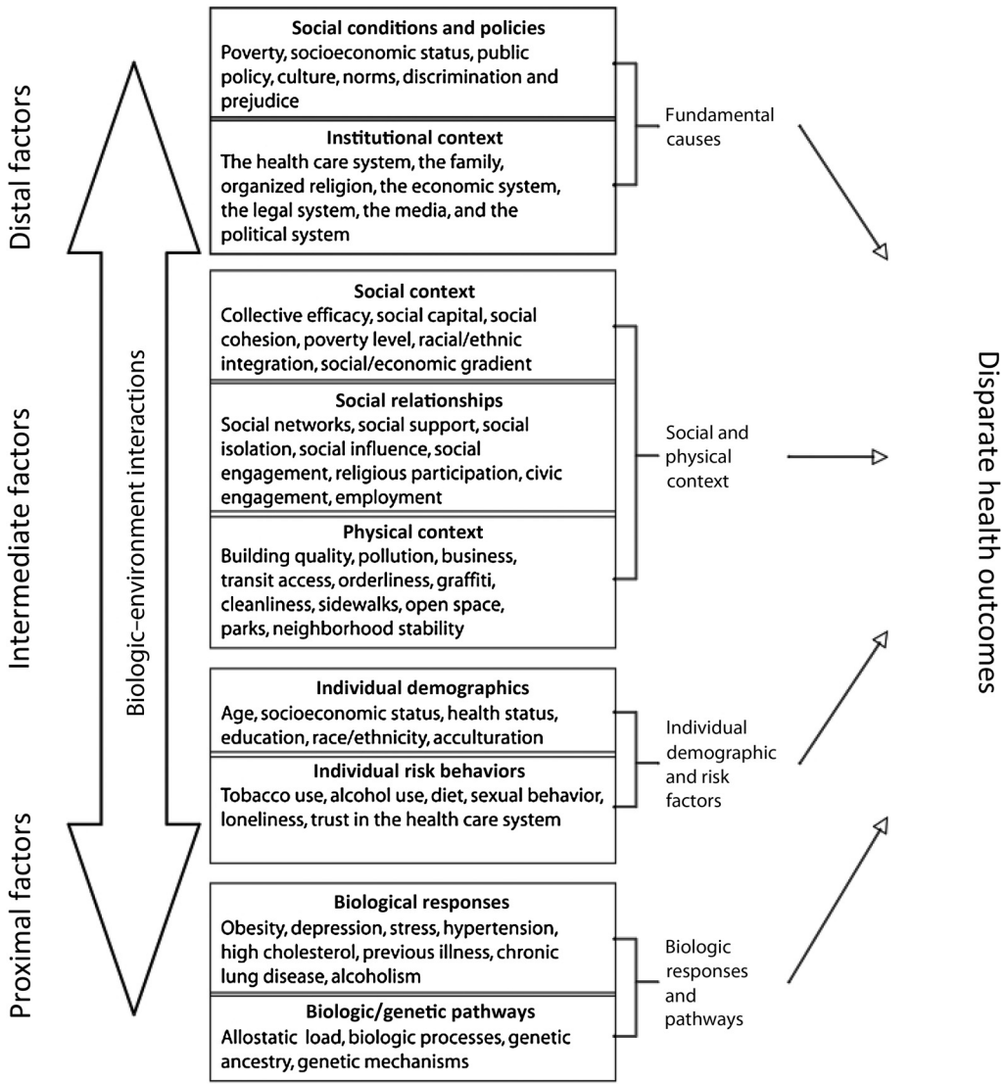

Figure 1.
Model for analysis of population health and health disparities. Source: Warnecke and colleagues, Approaching health disparities from a population perspective: the NIH Centers for Population Health and Health Disparities. Am J Public Health. 2008; 98:1608–15.

CARE 1

CARE 1 (2003–2008) was focused on determining why women living in Appalachia have an elevated burden of cervical cancer.

Project 1 (Lay health advisor to improve pap smear utilization: Project Director, E.D. Paskett, PhD; ref. 8)

Women from 14 clinics located in Ohio Appalachia who were in need of a Pap test were randomized to receive either usual care or a lay health advisor (LHA) intervention over a 10-month period. A total of 286 women enrolled into the study, 145 randomized in the LHA intervention and 141 randomized to usual care. Those in the LHA intervention received two in-person visits with a LHA, two phone calls, and four post cards, matched to Stage of Change (12) or readiness to obtain screening. The LHA assessed cervical cancer risk and addressed barriers to receiving a Pap test. Women in usual care received a letter from their doctor and brochure about Pap tests. According to medical record review, more women (51.1%) in the LHA intervention group received a Pap test, compared with those randomized to usual care (42%; $P = 0.135$); however, this was not a statistically significant difference, perhaps due to the large number of missing medical records and smaller than expected effective sample size. Self-reported rates were also reported with again, more women (71.3%) in the intervention group reporting receipt of a Pap test (vs. 54.2% in the control group; $P = 0.008$).

Project 2 (Evaluation of a lay advisor cessation intervention: Project Director, M.E. Wewers, PhD; ref. 10)

Women from 14 clinics located in Ohio Appalachia who were self-reported users of tobacco on a daily basis were enrolled into one of two study arms. Participants enrolled into the intervention arm ($n = 147$) received a nurse-managed protocol, which incorporated nicotine replacement and behavioral counseling over a 10-week period, while control participants ($n = 155$) received a personal letter from their provider, which advised them to quit smoking and to request a clinic appointment to discuss smoking cessation. At 3 and 6 months of follow-up, self-reported as well as cotinine-validated quit rates were significantly higher among participants in the intervention group compared with participants in the control group ($P < 0.02$); however, this effect was decreased by 12 months.

Project 3 (Predictors of abnormal cervical cytology: Project Director, M.T. Ruffin, MD; refs. 9, 13)

Women in this study were recruited from 17 clinics located in Ohio Appalachia as they came for a routine Pap smear ($n = 1131$). A total of 1,116 women had adequate HPV results, of which 278 women had abnormal cervical cytology and 838 had normal cervical cytology. The overall prevalence of HPV in this study was 43.1% for any HPV, 33.5% for high risk HPV, and 23.4% for low risk HPV. The prevalence of high risk HPV was higher in Appalachia than that reported in the U.S. population (26.9%; ref. 9).

In CARE 1, it was also found that overall Appalachian women had high rates of abnormal Pap tests, high rates of smoking, higher rates of HPV infection, higher poverty, high rates of risky sexual behaviors (multiple sexual partners and early first intercourse), low rates of HPV vaccination uptake, fewer social contact among smokers, a genetic susceptibility to cervical cancer immunity due to psychosocial stress, high rates of binge drinking, as well as high rates of depression (6, 8–10, 13–16).

CARE 2

CARE 2 was funded for an additional 5 years to build upon the results of CARE 1. Results from the four projects comprising CARE 2 are summarized below. For the studies in CARE 2, a multi-level framework was utilized, utilizing downstream as well as upstream factors as potential contributors to the observed cervical cancer disparity in Ohio Appalachian women (**Fig. 1**; ref. 11). **Figure 2** describes the objectives of each project in CARE 2, as well as the domains and respective variables of the multi-level model (**Fig. 1**) which were investigated for each project.

Project 1 (Inherited alterations of TGFβ signaling components: Project Director, C.M. Weghorst, PhD; ref. 17)

Project 1 examined the potential for gene–environment interactions and cancer risk in Appalachian women diagnosed with invasive cervical cancer ($n = 163$ cases) versus healthy Appalachian women with normal Pap tests ($n = 842$ controls). Specifically, comparisons of polymorphic variants in the cervical carcinogenesis-linked *TGFβ* signaling cascade, along with demographic, behavioral, and environmental characteristics were evaluated between the groups. Results found numerous alleles with significant interactions, including *TP53* rs1042522 ($P = 0.02$), *TGFβ1* rs1800469 ($P = 0.02$) and smoking; *NQO1* rs1800566 ($P = 0.05$) and alcohol consumption; *TGFβR1* rs11466445 ($P = 0.034$), *TGFβR1* rs7034462 ($P = 0.013$), *TGFβR1* rs11568785 ($P = 0.008$) and sexual intercourse before the age of 18; and *NQO1* rs1800566 ($P = 0.04$) and Appalachian self-identity. Multivariable logistic regression results examining the association between variant genotypes and cancer status showed a 3.03-fold reduction in cervical cancer odds using an overdominant model. Similarly, an overdominant *TGFβ1* rs1800469/*TGFβR1* rs7034462 model showed decreased odds of cervical cancer (2.78-fold) in Appalachian women who did not have sexual intercourse prior to age 18. Overall, this study demonstrated novel contributions of *TGFβ* pathway–associated low-penetrance alleles on the risk of cervical cancer in Appalachian women, as well as an unexpected association suggested between a genetic feature and the complex social construct of Appalachian self-identification.

Project 2 (Social networks and tobacco use: Project Director, M.E. Wewers, PhD; ref. 16)

In Project 2, social networks and social relationships were investigated for their relationship in how they may assist female smokers in smoking cessation. Women were recruited from three counties within Ohio Appalachia to complete a cross-sectional survey to characterize social networks by smoking status. The survey assessed time networks (or social ties with whom the participant spent time) as well as advice networks (or social ties with whom the participant goes to for advice and feedback). A total of 408 participants were enrolled, of which 20.1% were current smokers. Results found that, compared with nonsmokers, current smokers had more smoking ties in their networks. Compared with nonsmokers, current smokers in advice networks had less daily contact with nonsmoking ties. Factors that were different between smoking groups included: age, as never and former smokers were older than current smokers ($P = 0.0008$); depression score, as former and never smokers had lower odds of depression compared to current smokers ($P = 0.016$); former and never smokers had lower odds of social influence compared with current smokers ($P = 0.001$), there was an increased odds of social participation among never and former smokers compared with current smokers ($P = 0.005$); and compared with current smokers, never and former smokers reported significantly lower neighborhood cohesions ($P = 0.04$).

Project 3 (HPV immunization response and stress: Project Director, M.T. Ruffin, MD)

Project 3 researched how social conditions, social relationships, and individual factors influence immunity to

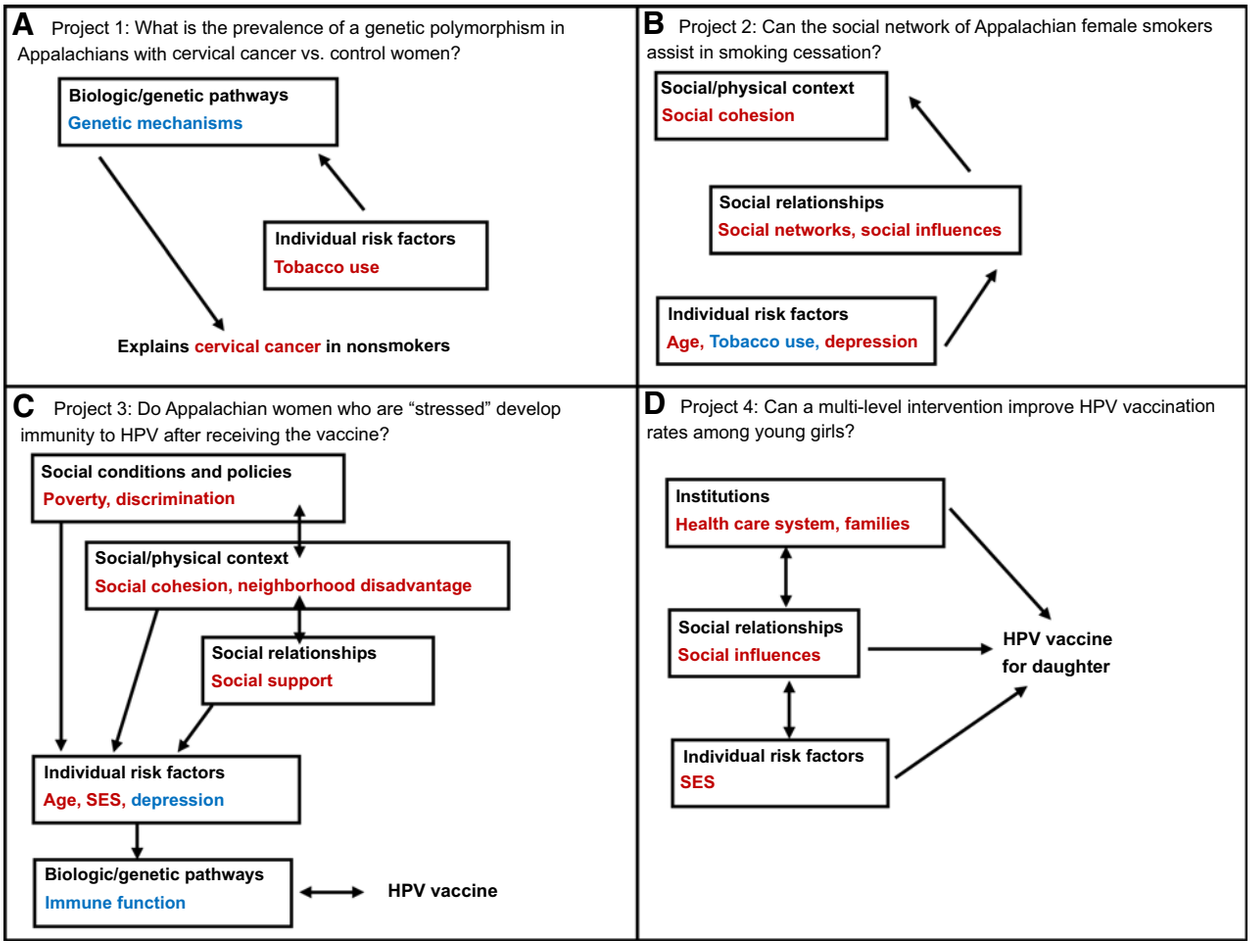

Figure 2.
A multi-level model for explaining cervical cancer disparities in Ohio Appalachia (CARE 2).

HPV. As mentioned above, in CARE 1 we found that women in Ohio Appalachia live in regions of low socioeconomic status (SES), low access to health care, and low social support, and used risky sexual behaviors, alcohol use, and smoking to cope with these situations. This allowed us to postulate a psychoneuroimmunology model of stress (**Fig. 2C**), where it was hypothesized that increased stress as well as depressive symptoms among Ohio Appalachian women would cause immune dysregulation and subsequent inadequate immune response to the Gardasil vaccine. A total of 185 women were enrolled, given Pap/HPV tests, had blood drawn for HPV titers, and received at least one dose of the HPV vaccine. A total of 146 women (79%) were followed through 12 months. At this time participants completed surveys, a Pap/HPV test, and had blood samples taken to test HPV and Epstein Bar virus (EBV) titers. The participating women's immune response was not impaired by prior or current HPV exposure, stress, smoking, depression, or evidence of immune dysregulation as measure by reactivation of EBV infection.

Project 4 (The PARENT project: Project Director, E.D. Paskett, PhD; ref. 18)

Project 4 investigated how institutions, social relationships, and individual risk factors influence whether or not parents will get the HPV vaccine for their daughter. The goal of this project was to develop and evaluate a multi-level HPV vaccine intervention to increase HPV vaccination rates among young girls and adolescent girls (9–17 years of age) living in Ohio Appalachia (the vaccine was only approved for girls at this time). A total of 12 Ohio Appalachian counties were included in this study, and counties were pair-matched on the basis of cervical incidence rates. One county from each pair of counties was randomized to receive an HPV vaccine intervention, whereas the other county was assigned to the comparison condition. Within these 12 counties, 24 clinics agreed to participate (10 intervention and 14 comparison). The clinic-level intervention focused on providing information about the HPV vaccination in waiting rooms and examination rooms within the clinics, including posters, brochures, and tabletop cards. Eligible parents were adult participants who had a daughter aged

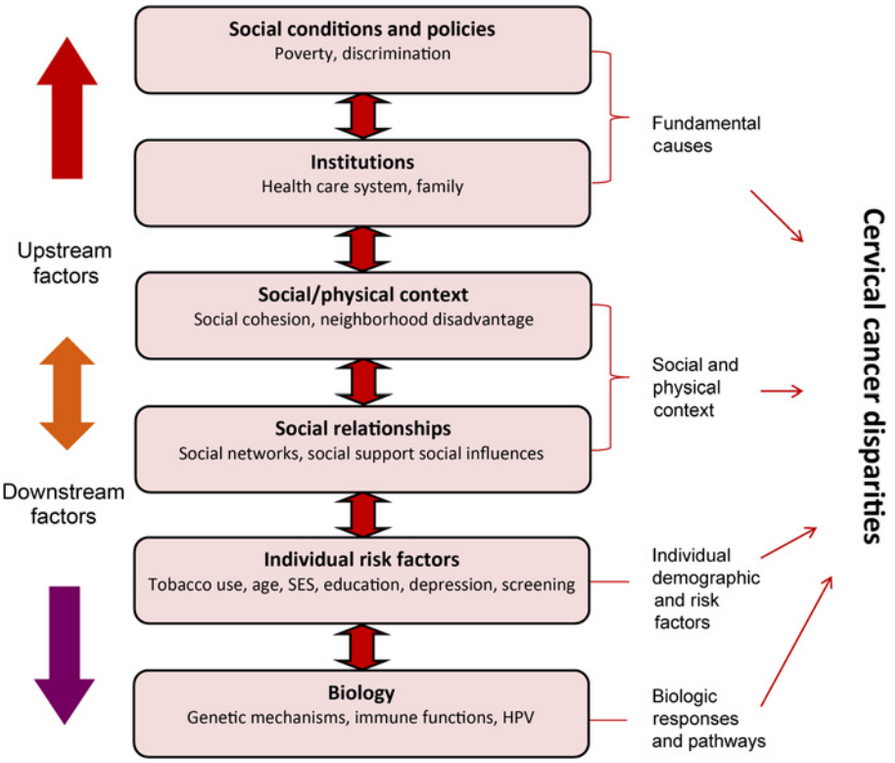

Figure 3.
Multi-level model for cervical cancer disparities in Ohio Appalachia.

9–17 years of age who had not received the HPV vaccine. Intervention participants were mailed a packet that contained an educational brochure as well as a DVD about HPV and the HPV vaccine, a magnet reminder to get the HPV shot, and an HPV vaccine information statement. Participants in the comparison group received informational packets that contained information regarding the flu vaccination. Overall, uptake of the HPV vaccine was low, although 10 daughters of intervention participants received the HPV vaccination within 3 months compared with four daughters of intervention participants in the comparison group ($P = 0.045$). Within 6 months, 17 daughters of participants in the intervention group received the HPV vaccine, compared with eight in the comparison group ($P = 0.003$).

Model for Explaining Cervical Cancer Disparities in Appalachia

Each project served to investigate separate domains of the multi-level model to understand cervical cancer disparities in Ohio Appalachian women. As shown in **Fig. 2**, variables within each relevant domain for each project are bolded. For example, Project 1 found novel associations between common low-penetrance alleles in the *TGFβ* signaling cascade, smoking status, and modified cervical cancer risk (**Fig. 2A**). Project 2 found that tobacco use was impacted by social networks, social cohesion, and social influences, as well as age and depression (**Fig. 2B**). Project 3 upon examining the effects of depression on immune function identified age, SES, social support, social cohesion, neighborhood disadvantage, poverty, and discrimination as important to immune functioning and full immune response to the HPV vaccine (**Fig. 2C**). Finally, Project 4 identified factors related to the uptake of the HPV vaccine in adolescents, mainly SES, social influences, healthcare system influences, and families (**Fig. 2D**). When assembled in a multi-level model, a picture emerges as to the explanations of cervical cancer disparities in Ohio Appalachia (**Fig. 3**) including: biology: genetic mechanisms, immune functioning, and HPV infection; individual risk factors: tobacco use, age, SES, education, depression, and cervical cancer screening; social relationships: social networks, social support, and social influences; social/physical context: social cohesion and neighborhood disadvantage; institutions: health care system and family; and social conditions and policies: poverty and discrimination.

Conclusions

This model of cervical cancer disparities in Appalachia has identified opportunities for intervention. Future funded projects will focus on implementation science strategies involving collaborative efforts with Ohio State University, University of Virginia, University of Kentucky, and University of West Virginia with an overall goal of addressing the burden of cervical cancer morbidity and mortality in Appalachia using a clinic-based implementation science multi-focal strategy (P01 CA229143). The aims of this program project include (i) conducting multi-level assessments to refine and validate a

logic model that will guide a family-based approach aimed at reducing cervical cancer; (ii) testing the overall effectiveness of three practice-based interventions implemented as a prevention program at the clinical level among patients who need an HPV vaccine, women who need a Pap test, and women who smoke; and (iii) to evaluate the impact of each project and the entire integration risk reduction program.

The program project will take place in 10 federally qualified health centers in Ohio, West Virginia, Kentucky, and Virginia Appalachia. If successful, this approach could be disseminated to other sites and clinics for cervical cancer risk reduction as well as to address other health disparities with a novel and innovative program that addresses multi-level disparities for specific conditions and regions. Such tailored and comprehensive strategies are needed to reduce and eliminate disparities across health conditions, populations and geographic areas.

Disclosure of Potential Conflicts of Interest

E.D. Paskett reports receiving a commercial research grant from Merck Foundation, other commercial research support from Merck Foundation, and has ownership interest (including patents) in Pfizer. No potential conflicts of interest were disclosed by the other authors.

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