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The significantly lower risk of cervical cancer at and after the recommended age to begin and end screening compared to breast and colorectal cancer ☆

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ABSTRACT

Objective. We compare risk of cervical, colorectal, and breast cancer (and two pre-cancers: cervical intraepithelial neoplasia (CIN) grade 2–3 and colorectal adenomas) at and after the recommended ages to begin and end screening in the United States.

Methods. Surveillance, Epidemiology, and End Results data were used with Monte Carlo simulations to estimate risk at and after the ages to screen.

Results. At the age to begin screening, absolute risk of breast and colorectal cancer was 381 and 53 times higher, respectively, than cervical cancer (0.0122, 95% CI: 0.0089–0.0162 and 0.0017, 95% CI: 0.0012–0.0023 vs. $3.2e^{-5}$, 95% CI: $2.3e^{-5}$–$4.3e^{-5}$). Risk of colorectal adenomas and breast cancer was 45 and 2.4 times higher than CIN 2–3 (0.2319, 95% CI: 0.1287–0.3624 and 0.0122, 95% CI: 0.0089–0.0017 vs. 0.0051, 95% CI: 0.0029–0.0081). After the age to end screening, breast and colorectal cancer risk was 17 and 11 times higher, respectively, than cervical cancer.

Conclusions. Risk of cervical cancer at and after the recommended ages for screening is significantly lower than that of breast and colorectal cancer. Differences may become more pronounced in the era of HPV vaccines. Comparison of risk between cancers provides a novel perspective to inform future guideline development.

Introduction

Several agencies in the United States provide detailed screening guidelines for cervical pre-cancer and cancer, including the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Society for Clinical Pathology (ASCP), the American Congress of Obstetricians and Gynecologists (ACOG), the United States Preventive Services Task Force (USPSTF), and the American Cancer Society (ACS). The USPSTF and the ACS have also developed screening guidelines for breast and colorectal cancer. When comparing across cancer type, current guidelines for these three cancers vary in terms of the age to begin screening (21 for cervical, and 50 for breast and colorectal), the frequency of screening (ranging from every year to every 10), and the age to end screening (65 for cervical, and 75 for breast and colorectal) (Table 1) (Smith et al., 2014; United States Preventive Services Task Force, 2008, 2009; Moyer and United States Preventive Services Task Force, 2012). Notably, for each cancer type, guidelines are consistent with the age to begin and end screening except for the age to begin breast cancer screening, with the ACS recommending mammography earlier at age 40.

Cancer guidelines are developed by groups of experts who systematically synthesize the evidence concerning the benefits and harms of screening with the underlying goal of providing clinicians with evidence-based recommendations (Harris et al., 2001). While the 2012 ACS–ASCCP–ASCP cervical cancer guidelines were developed using this approach, these guidelines also sought to more explicitly incorporate risk of cancer and pre-cancer (Saslow et al., 2012). Specifically, risk thresholds were used to compare risks associated with different tests and screening intervals with the goal of ensuring that similar recommendations were made for similar levels of risk. Similarly, updated USPSTF recommendations for the age to begin and end cervical cancer screening (21 and 65, respectively) were also based, in part, on the

Abbreviations: USPSTF, United States Preventive Services Task Force; ACS, American Cancer Society; ASCCP, American Society for Colposcopy and Cervical Pathology; ASCP, American Society for Clinical Pathology; ACOG, American Congress of Obstetricians and Gynecologists; SEER, Surveillance, Epidemiology, and End Results; Pr, probability; T+, test positive; T−, test negative; D+, disease positive; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia.

☆ Disclaimers: The authors declare that they have no competing interests.

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Table 1
United States cancer screening guidelines with estimates and ranges for test accuracy.

Test accuracy	Sensitivity	Specificity
Cervical cancer: cytology every 3 years women age 21 to 65, or cytology and HPV testing every 5 years for women 30 to 65[a]		
Cytology (cancer)	0.98 (0.96–1.00)	0.98 (0.96–1.00)
Cytology (pre-cancer)	0.58 (0.20–0.77)	0.92 (0.85–0.99)
Breast cancer: Biennial mammography screening for women aged 50 until age 75[b]		
Mammography (Cancer)	0.85 (0.71–0.98)	0.95 (0.94–0.97)
Colorectal cancer: three strategies were assessed as equally effective: fecal occult blood testing (every 1 year), or sigmoidoscopy (every 5 years), or colonoscopy (every 10 years) from age 50 to 75[c]		
Hemoccult II fecal test (cancer)	0.40 (0.25–0.50)	0.98 (0.95–0.99)
Colonoscopy (cancer)	0.95 (0.92–0.99)	0.90 (0.85–0.95)
Hemoccult II fecal test (pre-cancer)	0.06 (0.05–0.14)	0.98 (0.95–0.99)
Colonoscopy (pre-cancer)	0.85 (0.80–0.92)	0.90 (0.85–0.95)

Note: For each cancer type guidelines are consistent with regard to when to begin and end screening except for the age to begin breast cancer screening, with the ACS recommending mammography at an earlier age (40 years).
[a] Nanda et al. (2000), Koliopoulos et al. (2007), Mayrand et al. (2007), Vesco et al. (2011b).
[b] Humphrey et al. (2002).
[c] Zauber et al. (2008).

comparison of risk of cancer and pre-cancer at different ages. While guidelines are based on comparing risk within a given cancer, to our knowledge, formal comparisons of risk across other screen-detected cancers have not been conducted. Thus, it is unclear to what extent guidelines are consistent when examining risk across these cancers. Importantly, differences between cancers are expected due to distinct natural histories, the types of available screening tests and treatment options, and how these factors collectively affect cancer morbidity and mortality. However, this type of comparison may provide a novel perspective of risk that could be especially useful in informing future discussions regarding the age to begin cervical cancer screening given the availability of human papillomavirus (HPV) vaccines which are predicted to reduce cervical cancer by 70–90% (Munoz et al., 2003; Kjaer et al., 2009; Kirby, 2015).

The aim of this study is to compare the risk of cervical cancer with that of breast and colorectal cancer at and following the recommended ages to begin and end screening to provide an additional comparative perspective and encourage more explicit consideration of how risk thresholds should be defined in the era of HPV vaccines.

Methods

To compare guidelines we: 1) estimated the risk of cancer at the age to begin screening; 2) estimated the probability of cancer given a positive result and the probability of cancer given a negative result; and, 3) quantified the risk of cancer after the recommended age of screening cessation. Steps one and two of this approach were repeated for pre-cancerous cervical intraepithelial neoplasia (CIN) grades 2–3 and colorectal adenomas. For this analysis 'risk' refers to absolute risk defined as the probability of cancer for a specific population at a given age.

Risk at the recommended age to begin screening

To estimate risk at the age to begin screening we calculated period prevalence, under the assumption that cases would accumulate over time until initiation of screening. Prevalence was calculated using 2008 data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program (Surveillance, Epidemiology, and End Results (SEER) Program, 2012). For each cancer the numerator was calculated by summing cases occurring during a five-year age range prior to and including the recommended age to begin screening. This approach results in the cumulative number of cancers that would be present at the recommended age to start screening. Only the first tumor occurrence for the site of interest during 2008 was included in risk estimates. The denominator was estimated as the number of people residing in SEER participating areas who were of the age to begin screening. For example, breast cancer cases occurring among women between and including the ages of 46 to 50 were summed and divided by the number of 50 year old women living in SEER areas during 2008. Ductal carcinoma in situ cases (DCIS) were excluded from estimates of breast cancer risk given debate related to classifying this condition as cancerous (Punglia et al., 2013). DCIS cases were identified using International Classification of Diseases for Oncology coding (Patel et al., 2003). Additionally, as cervical and colorectal cancer screening can detect pre-cancerous conditions, estimates of pre-cancer prevalence at the age to begin screening were included in the analysis (Zauber et al., 2008; Kulasingam et al., 2013). Estimates of risk at the recommended age to begin screening were externally validated by comparison to those reported elsewhere (Merrill et al., 2000; Vesco et al., 2011a; Decew et al., 2013; Siegel et al., 2014; Rositch et al., 2014). Using the methods described above, we also estimated the risk of cervical cancer at age 25 due to interest in delaying screening based on evidence that screening in women age 20–24 has little impact on cervical cancer rates up to age 30 (Vesco et al., 2011a; Benard et al., 2012; Bouchard-Fortier et al., 2013; Esserman et al., 2013; Sasieni et al., 2009, 2010). Furthermore, we examined the risk of breast cancer at age 40 to account for differences between the USPSTF and ACS breast cancer screening guidelines (Smith et al., 2014).

To explore the impact of uncertainty in estimates of risk at the recommended age to begin screening, two additional methods were used. First, the numerator was calculated by summing cases occurring in a ten year age range prior to and including the age to begin screening. Second, the numerator for each cancer was calculated by summing cases occurring among a ten year age range covering 5 years prior to and after the age to begin screening. This resulted in estimates of risk that were larger than the base estimates used for the primary analysis.

Screening performance at the recommended age to begin screening

To examine the performance of initiating screening at the recommended ages, we used estimated ranges for test accuracy reported in the literature (Zauber et al., 2008; Humphrey et al., 2002; Nanda et al., 2000; Koliopoulos et al., 2007; Mayrand et al., 2007; Vesco et al., 2011b). These tests included mammography for breast cancer, cytology for CIN 2–3 and cervical cancer, as well as flexible sigmoidoscopy, colonoscopy, and stool tests for colorectal adenomas and cancer. As several types of screening tests for colorectal cancer are included in the guidelines, we chose the most accurate (colonoscopy) and the least accurate (Hemoccult II fecal occult blood testing) to bound estimated results. We applied different sensitivity and specificity estimates based on whether a test was used to detect cancer or pre-cancer. For each condition, the probability of having cancer or pre-cancer given a negative result ($Pr(D+|T-)$) and the probability of having cancer or pre-cancer given a positive result ($Pr(D+|T+)$) were estimated.

Estimating risk after the recommended age to end screening

We determined the risk of invasive cancer after the recommended age to end screening using SEER age-specific lifetime risk estimates (Howlader et al., 2012). These estimates represent the lifetime risk of being diagnosed with cancer for those who are alive and cancer-free at a given age. SEER estimates for cervical cancer do not account for hysterectomy prevalence, resulting in the underestimation of risk. Therefore, the cervical cancer lifetime risk estimate was adjusted to account for an estimated 45% hysterectomy prevalence among women above the age of 65 (Rositch et al., 2014).

Analysis

To account for uncertainty, we varied each cancer risk estimate by 30% to create a lower and upper bound. As estimates of pre-cancer risk were based on simulation models, we varied each estimate by 50% to account for greater uncertainty. Ranges for test sensitivity and specificity were based on low and high estimates reported in the literature (Zauber et al., 2008; Humphrey et al., 2002; Nanda et al., 2000; Koliopoulos et al., 2007; Mayrand et al., 2007; Vesco et al., 2011b). Beta distributions were generated for estimates of risk, sensitivity, and specificity. To generate 95% credible intervals for probability estimates, Monte Carlo simulations with 100,000 samples were conducted for each screening scenario using TreeAgePro 2014 (Williamstown, MA). Results were compared in terms of the magnitude of difference, such that they were considered similar if they were within an order of magnitude (e.g., 0.05 and 0.09) or different if they varied by more than an order of magnitude (e.g., 0.05 and 0.005).