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*Lancet Gastroenterol Hepatol* 2019 May 16

#### **Young-Onset Colorectal Cancer: A Disease**

*The incidence of colorectal cancer in individuals younger than 50 is rising in several developed countries.*

Epidemiologic data from the United States show rising colorectal cancer (CRC) incidence in individuals younger than 50. Two studies report the epidemiology of young-onset CRC in other countries.

In one study, investigators assessed CRC incidence and mortality in about 144 million people aged 20 to 49 years from 20 European countries. In individuals aged 20 to 29, CRC incidence increased from 0.8 to 2.3 cases per 100,000 persons between 1990 and 2016. The increase accelerated from 1.7% (1990–2004) to 8% per year (2004–2016). There were similar trends in older age groups, but the annual increases between 2004 and 2016 were less marked (5% for 30- to 39-year-olds and 1.6% for 40- to 49-year-olds). Overall, colon cancer incidence rose more than rectal cancer incidence. The CRC incidence increases in the 30 to 39 and 40 to 49 age groups started 10 to 20 years after incidence rose in the 20 to 29 group, consistent with a birth cohort effect.

Another study reports colon and rectal cancer registry data from Australia, Canada, Denmark, Norway, New Zealand, Ireland, and the U.K. Colon cancer incidence in individuals younger than 50 increased between 2% and 3% in Denmark, New Zealand, Australia, and the U.K over 10 years. Similar trends were observed for rectal cancer incidence in Canada,

Australia, and the U.K. Incidence rate ratios showed increasing trends in successive generations in all countries, which were more marked for rectal cancer.

**COMMENT:** These data provide compelling support to the notion that young-onset CRC is predominantly a disease of affluence. The fact that CRC incidence is increasing in individuals younger than 50 in many developed countries, along with the birth cohort effects, suggests that the “Western lifestyle” is a prime suspect. While the mechanisms driving these trends remain unclear, there are several likely contributing and interrelated factors, such as overweight, red and processed meat consumption, smoking, lack of physical activity, gut microbiome alterations, and environmental factors. The epidemiologic trends do not support universal CRC screening in younger persons, because the absolute rates remain significantly lower than in those 50 and older, although some argue that decreasing the screening start age is an inevitability in the long run. In the meantime, clinicians should continue to focus on modifiable risk factors and consider screening for higher-risk individuals and those with symptoms.

**CITATION(S):** Vuik FER et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019 May 16; [e-pub]. (<https://doi.org/10.1136/gutjnl-2018-317592>)

Araghi M et al. Changes in colorectal cancer incidence in seven high-income countries: A population-based study. *Lancet Gastroenterol Hepatol* 2019 May 16; [e-pub]. ([https://doi.org/10.1016/S2468-1253\(19\)30147-5](https://doi.org/10.1016/S2468-1253(19)30147-5))

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*N Engl J Med* 2019 Jun 2

## **Enzalutamide for Hormone-Sensitive Metastatic Prostate Cancer**

*Survival was significantly prolonged by combining standard ADT with enzalutamide than with a first-generation androgen-receptor.*

Level-1 evidence indicates that adding docetaxel, abiraterone, or apalutamide to standard androgen-deprivation therapy (ADT) can improve overall survival (OS) in many men with hormone-sensitive metastatic prostate cancer (HSMPC).

Now, international investigators have conducted an industry-funded, open-label, randomized, phase III study involving 1125 men with HSMPC (median age, 69 years) to compare the value of adding a next-generation androgen-receptor inhibitor (enzalutamide) to ADT versus adding a first-generation androgen-receptor inhibitor (bicalutamide, nilutamide, or flutamide) to ADT (control group). The protocol was modified after enrollment of 88 patients to allow patients to have previously received docetaxel for HSMPC.

At a median follow-up of 34 months, 3-year OS (the primary endpoint) was significantly longer in the enzalutamide group than in the control group (80% vs. 72%; hazard ratio, 0.67;  $P=0.002$ ), as were prostate-specific antigen (PSA) progression-free survival (PFS) and clinical PFS. These results were not affected by volume of disease or prior use of docetaxel. At 3 years, the percentage of patients still receiving a trial regimen was 62% in the enzalutamide group and 34% in the control group. Fatigue and seizures were more common with enzalutamide.

**COMMENT:** In this well-conducted study, the benefit of enzalutamide on OS was not affected by prior receipt of docetaxel or subsequent therapies. The authors note that the effect of enzalutamide on OS appeared smaller in the subgroup receiving prior docetaxel, but that the study was not powered to address this issue. There is a therapy burden associated with enzalutamide that must be considered by clinicians and patients as they review the evolving treatment options in this clinical space. Longer follow-up of this trial will likely provide important information.

**CITATION(S):** Davis ID et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019 Jun 2; [e-pub]. (<https://doi.org/10.1056/NEJMoa1903835>)

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*JAMA Intern Med* 2019 Jun 10

## Turn Off the Lights (and the TV) Before Going to Sleep

*A large observational study suggests exposure to artificial light at night while sleeping raises risk for obesity.*

Animal and limited human data indicate that exposure to artificial light at night (ALAN) contributes to obesity. As part of a prospective U.S. cohort study, 43,222 women (mean baseline age, 55) were asked about sources of ALAN present while sleeping, including no light (Category 1 [C1]), a nightlight or clock radio (C2), light from outside the room (C3), or a television or  $\geq 1$  light on in the room (C4). Body-mass index (BMI) was measured at baseline and every 2 to 3 years.

Baseline mean BMI progressively increased with ALAN exposure, from 27.0 kg/m<sup>2</sup> (C1 and C2) to 29.2 (C4). In analysis adjusted for several covariables, having any ALAN exposure was associated with higher prevalence of obesity at baseline (prevalence ratio, 1.03). At a mean follow-up of 5.7 years, any ALAN exposure was also associated with incident obesity (relative risk, 1.19). Compared with C1 ALAN, C4 ALAN was associated with gaining  $\geq 5$  kg (RR, 1.17;  $P < 0.001$  for both trends).

**COMMENT:** Exposure to ALAN may suppress melatonin production, disrupting circadian rhythms. However, as the authors also note, ALAN exposure while sleeping may simply reflect socioeconomic disadvantage and unhealthy lifestyles associated with obesity. Either way, counseling our patients to minimize nighttime exposure to artificial light seems eminently reasonable.

**CITATION(S):** Park Y-MM et al. Association of exposure to artificial light at night while sleeping with risk of obesity in women. *JAMA Intern Med* 2019 Jun 10; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.0571>)

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*A nationwide cross-sectional study. Menopause* 2019 Jun; 26:598

## What Might Menopausal Hormone Therapy Have to Do with Knees?

*Korean cross-sectional study found lower prevalence of knee osteoarthritis in HT users than in nonusers.*

Osteoarthritis (OA) is more common in women than men, and its prevalence rises after menopause. Diverse evidence suggests that menopausal hormone therapy (HT) attenuates OA symptoms and may reduce OA incidence. Using 2009–2012 data from a nationally representative Korean cross-sectional study, investigators evaluated outcomes in 4766 women over 50 in whom x-ray imaging of the knee joint had been performed. Knee OA was defined based on reported symptoms and radiologic findings; HT users were defined based on use for  $\geq 12$  months. Four distinct regression models were adjusted for various parameters.

Compared with nonusers of HT, users had lower risk for knee OA (odds ratio, 0.59; 95% confidence interval, 0.45–0.78). In each model, the OR for OA was significantly lower among HT users.

**COMMENT:** Estrogen can reduce musculoskeletal pain and prevent damage to cartilage — and these Korean findings suggest that menopausal HT can prevent OA. One limitation of this observational study is that the Korean population is ethnically homogenous, limiting the generalizability of the conclusion. Most participants used combination estrogen-progestin HT, suggesting that progestin does not neutralize estrogen's benefits regarding OA. Prospective clinical trials should aim to establish causality and characterize HT's efficacy in the setting of this common condition.

**CITATION(S):** Jung J et al. Knee osteoarthritis and menopausal hormone therapy in postmenopausal women: A nationwide cross-sectional study. *Menopause* 2019 Jun; 26:598. (<https://doi.org/10.1097/GME.0000000000001280>)

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*Cancer Prev Res (Phila)* 2019 May; 12:305

## **Sobering Numbers About Smoking and Bladder Cancer**

*Data from postmenopausal women drive home the concept that it's never too late to quit.*

Smoking is the strongest predictor of bladder cancer, which is the fourth and ninth most common malignancy among U.S. men and women, respectively. Although risk for bladder cancer is lower among former than among current smokers, the degree of risk reduction after quitting remains uncertain. Investigators analyzed combined data from the Women's Health Initiative clinical trial and observational studies (143,279 women; age range: 50–79 at enrollment; 53%, 40%, and 7% were never, former, and current smokers, respectively).

In all, 870 bladder cancers were diagnosed during mean follow-up of 15 years. Adjusted for age, compared with never smokers, former and current smokers' risks for bladder cancer were 2.0 and 3.4, respectively. In analysis adjusted for several additional factors, risk fell with increasing years since quitting (hazard ratio, 2.77 [ $<10$  years], 2.19 [10 to  $<20$  years], and 1.96 [20 to  $<30$  years];  $P$  for trend,  $<0.0001$ ).

**COMMENT:** The marked association between bladder cancer and smoking provides another talking point with patients, regarding the importance of cessation — and this high-quality study provides additional support for the concept that it's never too late to quit. In addition, this report reminds us how common bladder cancer is. We occasionally see cases in which diagnosis is delayed because a clinician fails to fully evaluate middle-aged and older adults (women or men) with otherwise unexplained microscopic or visible hematuria.

Since its initial publication in NEJM Journal Watch on May 13, 2019, this summary has been updated with additional details from the original study.

**CITATION(S):** Li Y et al. Smoking cessation and the risk of bladder cancer among postmenopausal women. *Cancer Prev Res (Phila)* 2019 May; 12:305. (<https://doi.org/10.1158/1940-6207.CAPR-18-0441>)

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*JAMA Pediatr* 2019 May 28

## **Treat Adolescents with STIs Before Discharging Them from the ED**

*This retrospective study found that almost half of adolescents prescribed outpatient antibiotics for pelvic inflammatory disease or chlamydia did not fill their prescriptions.*

Sexually transmitted infections (STIs) are common in adolescents and may lead to significant complications, including abscesses, infertility, and ectopic pregnancies. Although STIs such as chlamydia are easily treated with antibiotics, it is unknown how frequently adolescents actually fill these prescriptions.

Using pharmacy and insurance plan data, researchers retrospectively assessed the proportion of antibiotic prescriptions filled by adolescent girls and boys (ages 13 to 19 years) treated for pelvic inflammatory disease or chlamydia at one of two pediatric emergency departments (EDs) in Washington, DC, between 2016 and 2017. Of 208 patients who were prescribed outpatient antibiotics, only 58% of prescriptions were filled. Patients who were hospitalized were more likely to fill their prescription.

**COMMENT:** This study suggests that many adolescents do not fill their antibiotics for STIs, which could lead to subsequent complications as well as prolonged transmission to partners. It is possible that the database used in this study may not have captured all medication fills, thereby underestimating the antibiotic fill rate; however, it is also likely that patients who fill prescriptions may not take the entire course of medication. Given that many STIs can be treated with a single dose of medication, we should administer antibiotics in the ED prior to discharge.

**CITATION(S):** Lieberman A et al. Frequency of prescription filling among adolescents prescribed treatment for sexually transmitted infections in the emergency department. *JAMA Pediatr* 2019 May 28; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.1263>)

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*Pediatrics* 2019 Jun 10

## **Childhood Shingles Incidence in the Chicken Pox Vaccination Era**

*Varicella zoster vaccine reduced risk for subsequent herpes zoster by 72% between 2003 and 2014.*

Herpes zoster (HZ) is a result of reactivation of varicella zoster virus (VZV) sometime after chicken pox, the primary infection caused by the virus. Although the incidence of HZ is lower in children than in adults, it is well described, and children with primary VZV before age 1 year are at greatest risk. Children can also develop HZ after vaccination, but the risk for reactivation following vaccination has been challenging to study, requiring a large number of children infected with vaccine-type virus (vaccinated) and wild-type virus (unvaccinated).

In this study, researchers assessed physician-documented HZ incidence and VZV vaccination status during 2003 to 2014 among 6.4 million children enrolled in six healthcare organizations. Results include the following:

- Overall, 50% of children were vaccinated for VZV during the study period; this rate increased over time, reaching 91% in 2014.
- Incidence of HZ was 74 per 100,000 (61 per 100,000 for laboratory-confirmed HZ) and declined by 72% over time.
- HZ incidence was 78% lower in vaccinated children (38 per 100,000) than in unvaccinated children (170 per 100,000).
- Among 1-year-olds, vaccinated children had a higher HZ rate than unvaccinated children, but among children aged 5–17 years, vaccinated children had a significantly lower risk for HZ than unvaccinated children.
- Children vaccinated with two VZV vaccine doses, as is recommended, had 50% lower risk for HZ compared with those who had received just one dose.

**COMMENT:** This vaccine does double duty: in addition to protecting children from varicella zoster infection, and all the complications that can result, the vaccine significantly reduces the incidence of herpes zoster. Although further evidence supporting the benefits of vaccinating children should not be necessary, these findings provide just that.

**CITATION(S):** Weinmann S et al. Incidence of herpes zoster among children: 2003–2014. *Pediatrics* 2019 Jun 10; [e-pub]. (<https://doi.org/10.1542/peds.2018-2917>)

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## Different Types of Maltreatment in Childhood, Different Emotional Responses in Adolescence

*The neurophysiological impact of abuse may differ from the impact arising from neglect.*

Childhood maltreatment and other adverse childhood experiences (ACEs) have been linked to poor neurodevelopmental outcomes, psychopathology, and physical health problems in adulthood; individuals exposed to severe stressors during early development have altered brain structure and function. To determine whether different forms of maltreatment lead to distinct physiological or clinical outcomes, investigators looked for associations between childhood maltreatment and emotional responding in 116 adolescents (60% male; age range, 10–18 years), recruited from a residential care setting or the surrounding community.

To quantify maltreatment exposure, the researchers used a standardized self-report questionnaire capturing emotional, physical, or sexual abuse and emotional or physical neglect. Overall, 87% of participants reported some prior maltreatment, 54% of whom met the threshold for significant maltreatment. Functional MRI captured brain activation as participants completed a Stroop task, in which they attended to the number of numerals displayed between presentation of images with negative, neutral, or positive affect.

Greater amounts of maltreatment were associated with lesser differential responsiveness to both congruent trials (the numeral matched the number of times it appeared on the display; e.g., four 4s) and incongruent ones (e.g., five 4s), compared with blank displays. The amount of abuse, but not neglect, was associated with greater activation of brain regions involved in response to affective information.

**COMMENT:** Severity of psychopathology correlates with severity of prior maltreatment, and abuse and neglect often occur in the same environment; therefore, disentangling these factors is difficult. Nevertheless, the finding that being assaulted is differentially toxic from being neglected has face validity and might be clinically predictive. Against a backdrop of the growing interest in adverse events in childhood, this study underscores that all ACEs may not be equal.

**CITATION(S):** Blair KS et al. Association of different types of childhood maltreatment with emotional responding and response control among youths. *JAMA Netw Open* 2019 May 24; 2:e194604. (<https://doi.org/10.1001/jamanetworkopen.2019.4604>)

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## One Reason Why Vulnerable Adolescents Should Not Watch *13 Reasons Why*

*A 3-month spike in suicides among adolescents ages 10 to 19 was seen after the show's release.*

Many adolescents binge-watched the 13 episodes of the Netflix show *13 Reasons Why*, consisting of recordings made to various people about the reasons why a fictional 17-year old female high school student died by suicide. Researchers examined CDC suicide statistics after the show's release for individuals in three age groups — 10–19 years, 20–29, and  $\geq 30$  — and, as a proxy for public interest, posts on Twitter and Instagram, which are visited by at least three fourths of U.S. adolescents.

In analyses correcting for seasonal and temporal changes in rates of suicide, suicide rates in only the 10–19 age group (the target audience) increased during the 3 months after the show's release, with a peak in the first month and a return to baseline after 3 months. The percentage was higher in females (22%) than males (12%); hanging was the most frequent method. Social media posts increased in parallel with suicides.

**COMMENT:** Although the results do not prove that the show was responsible for the spike in suicides, the temporal association with the show and the concomitant increase in social media posts strengthen this suspicion. The main character cut her wrists, but people on social media discussed the low lethality of this method, raising the possibility that suicidal adolescents therefore tried the more deadly method of hanging. Editorialists note that because people pay more attention to negative events, media outlets focus on these, potentially influencing a small percentage of the public but a sizable number of vulnerable individuals and thus fueling epidemics of self- or other-directed violence. Clinicians should monitor their patients' responses to similar media events.

**CITATION(S):** Niederkrotenthaler T et al. Association of increased youth suicides in the United States with the release of *13 Reasons Why*. *JAMA Psychiatry* 2019 May 29; [e-pub]. (<https://doi.org/10.1001/jamapsychiatry.2019.0922>)

VanderWeele TJ et al. Media portrayals and public health implications for suicide and other behaviors. *JAMA Psychiatry* 2019 May 29; [e-pub]. (<https://doi.org/10.1001/jamapsychiatry.2019.0842>)

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*Gastrointest Endosc* 2019 May 10

## Can Magnetic-Assisted Capsule Endoscopy Detect Upper GI Bleeding Lesions?

*The diagnostic yield was similar with capsule endoscopy versus standard endoscopy in a proof-of-concept study.*

Magnetic-assisted capsule endoscopy (MACE) is a real-time examination technique in which a hand-held magnet is used to control the position of a capsule containing a tiny camera that is swallowed by a patient. To determine the effectiveness of MACE in diagnosing upper gastrointestinal bleeding (UGIB), investigators in the U.K. conducted a prospective, single-blinded, cohort study in which 33 patients with suspected UGIB underwent a MACE examination followed by a standard endoscopy examination.

For the MACE exam, patients drank 1 liter of water containing simethicone and then swallowed the capsule while lying in the right lateral position. The magnet was used to steer the capsule and help view the esophagus as the patient completed a sequence of position changes. The MACE examination took 20 minutes to perform.

Compared with standard endoscopy, MACE detected more focal lesions (40 vs. 25) but had a similar yield of clinically significant lesions; MACE also found an additional cause for small bowel bleeding in 18% of patients. MACE missed one gastric ulcer and three duodenal bulb ulcers, including one requiring endoscopic therapy. Standard endoscopy missed one esophageal ulcer and 4 duodenal ulcers.

**COMMENT:** This small pilot study should be viewed as a proof-of-concept report. The need for substantial water ingestion, multiple patient position changes, and active magnetic manipulation of the capsule limit the current applicability of this technique. However, the concept of early patient triage with lesion identification by a relatively noninvasive method such as capsule endoscopy is appealing. In addition, this study further supports the early use of capsule endoscopy to detect bleeding lesions in the small bowel.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

**CITATION(S):** Ching HL et al. Magnetically assisted capsule endoscopy in suspected acute upper-GI bleeding versus esophagogastroduodenoscopy in detecting focal lesions. *Gastrointest Endosc* 2019 May 10; [e-pub]. (<https://doi.org/10.1016/j.gie.2019.04.248>)

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## Preoperative Albuterol Reduces Respiratory Complications in Pediatric Tonsillectomy

*Randomized, controlled trial results support routine use of pretonsillectomy albuterol.*

Children undergoing tonsillectomy frequently experience perioperative respiratory complications. Presurgical albuterol treatment has not shown benefit among children in a general surgical population but may help for airway-specific procedures such as tonsillectomy.

Researchers randomized 484 children aged 1 to 9 years undergoing tonsillectomy to receive two actuations of albuterol or placebo by inhaler just before surgery; group assignment was triple-blinded (researchers, treatment team, and patient). The primary outcome was incidence of any perioperative respiratory complication, and secondary outcomes were incidence of specific complications (bronchospasm, laryngospasm, coughing, oxygen desaturation <95%, obstruction, or stridor).

Children in the placebo group had significantly higher risk for any respiratory complication (48% vs. 28%; odds ratio, 2.4; number needed to treat [NNT], 4.8), laryngospasm (12% vs. 5%; OR, 2.5), coughing (33% vs. 11%; OR, 3.9), and oxygen desaturation (23% vs. 15%; OR, 1.7) compared with those in the albuterol group. Adjusting for obstructive sleep apnea (OSA) severity and airway type (endotracheal tube vs. laryngeal airway) resulted in slightly higher odds for any complication (OR, 2.8) and lower NNT (4.2). The increased odds of complications in the placebo group were magnified by presence of moderate or severe OSA (ORs, 3.0 and 5.3, respectively).

**COMMENT:** Albuterol is an inexpensive and safe medication that appears to substantially reduce the incidence of respiratory complications related to tonsillectomy. Although the authors speculate that albuterol use is likely to reduce hospital length of stay, unplanned intensive care unit admissions, and surgical schedule inefficiencies, these outcomes were not included in the study and need to be assessed in future investigations. In the meantime, routine use of pretonsillectomy albuterol should be considered based on these results alone, particularly in children with moderate or severe OSA.

**CITATION(S):** von Ungern-Sternberg BS et al. Effect of albuterol premedication vs placebo on the occurrence of respiratory adverse events in children undergoing tonsillectomies: The REACT randomized clinical trial. *JAMA Pediatr* 2019 Apr 22; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.0788>)

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