About UICC

The Union for International Cancer Control (UICC) is the leading international non-governmental organization dedicated to global cancer control. Founded in 1933, UICC unites over 300 member organizations, specialized and engaged in cancer control, in more than 100 countries across the world.

UICC’s mission is to connect, mobilize and support organizations, leading experts, key stakeholders and volunteers in a dynamic community working together to eliminate cancer as a life-threatening disease for future generations.

UICC works closely with its member organizations and partners to implement a comprehensive strategy that includes:

- promoting the World Cancer Declaration
- organizing the World Cancer Congress
- raising awareness through the World Cancer Campaign
- coordinating World Cancer Day annually, on 4 February
- reviewing and disseminating the TNM (tumour-node-metastasis) classification of malignant tumours
- developing effective cancer control programmes especially in low- and middle-income countries
- changing cancer-related beliefs and behaviour through information and education
- creating special initiatives in prevention, early detection, access to treatment and supportive care
- awarding international cancer fellowships
- producing cutting-edge scientific publications, such as the *International Journal of Cancer*

UICC is governed by its member organizations, which meet in a general assembly, held in conjunction with the World Cancer Congress, every two years. Between assemblies, a board of 17 directors, elected by the general assembly, acts as the executive body of the UICC.

UICC works closely with the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and the Programme of Action for Cancer Therapy (PACT) and has consultative status with the UN Economic and Social Council. It offers corporate partners a unique opportunity to demonstrate social responsibility on a global scale. Every two years.

UICC is non-profit, non-political and non-sectarian. Its headquarters are in Geneva, Switzerland. www.uicc.org

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Union for International Cancer Control

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Mini Review

1512 The role of metabolic reprogramming in γ-herpesvirus-associated oncogenesis
Angela Kwok-Fung Lo, Christopher W. Dawson, Lawrence S. Young, and Kwok-Wai Lo

1522 Suicidal death of erythrocytes in cancer and its chemotherapy: A potential target in the treatment of tumor-associated anemia
Elisabeth Lang, Rosi Bissinger, Syed M. Qadri, and Florian Lang

Cancer Epidemiology

1529 Socioeconomic and demographic disparities in breast cancer stage at presentation and survival: A Swiss population-based study
Anita Feller, Kurt Schmidlin, Andrea Bordoni, Christine Bouchardy, Jean-Luc Builiard, Bertrand Camey, Isabelle Konzelmann, Manuela Maspoli, Miriam Wanner, Kerri M. Clough-Gorr; for the SNC, the NICER working group
Switzerland ranks high internationally in measures of well-being, with citizens benefiting from universal health care. Nonetheless, according to this report, disparities in breast cancer (BC) survival remain. Analyzes of data from the Swiss National Cohort and the National Institute for Cancer Epidemiology and Registration cancer registry network show that women of lower socioeconomic position (SEP) are more likely to be diagnosed with later-stage BC and have a higher risk of dying from the disease than woman of higher SEP. Differences in survival were independent of socioeconomic and sociodemographic factors, suggesting possible involvement of other variations, such as in treatment or comorbidities.

1540 Impact of extending screening mammography to older women Information to support informed choices
Gemma Jacklyn, Kirsten Howard, Les Irwig, Nehmat Houssami, Jolyn Hersch, and Alexandra Barratt
In Australia, invitation to screening mammography recently was extended to women ages 50–74 years, whereas the previous age range was 50–69 years. Consequently, participation by older women has almost doubled. This study shows, however, that extending the upper age limit of screening mammography to 74 is likely to result in a small decrease in breast cancer mortality but a substantial increase in overdiagnosis. Analyses indicate that one additional breast cancer death, 78 false positives, and eight instances of overdiagnosis would occur for every 1,000 women screened biennially. The findings emphasise the importance of patient-clinician discussion and informed decision-making by screening-eligible women.

1551 Stratifying HPV-positive women for CIN3+ risk after one and two rounds of HPV-based screening
Nienke J. Veldhuijzen, Nicole J. Polman, Peter J.F. Snijders, Chris J.L.M. Meijer, and Johannes Berkhof
Testing for HPV infection has been widely adopted by cervical-cancer screening programs, along with cytology (Pap test). However, the authors of this study found that the prognostic value of HPV genotyping diminished after two rounds of HPV-based screening, while that for cytology remained the same. This was presumably due to a change in the proportion of HPV-positive women with short-term incident infections that may resolve quickly. Thus, revised guidelines for cervical-cancer triage may be needed in the future, to ensure more accurate screening.

1561 Cervical cancer incidence after up to 20 years of observation among women with HIV
L. Stewart Massad, Nancy A. Hessol, Teresa M. Darragh, Howard Minkoff, Christine Colie, Rodney L. Wright, Mardge Cohen, and Eric C. Seaberg
Women infected with HIV face higher risks for carcinogenic human papillomavirus (HPV) infection and pre-cancer. Longer life expectancy due to effective combination antiretroviral therapy may allow persistent HPV infections to progress to cancer. Here, the authors show that HIV infection only minimally raises invasive cervical cancer (ICC) risk when women are enrolled in care that includes intensive screening and protocol-based referral to treatment. Cervical cancer has not emerged as a major cause of morbidity and mortality in such a prevention program, underscoring the importance of regular screening and assiduous treatment of ICC precursors in women with HIV.
International variation in the prevalence of preclinical colorectal cancer: Implications for predictive values of noninvasive screening tests and potential target populations for screening
Agne Krilaviciute, Christian Stock, and Hermann Brenner

Colorectal cancer (CRC) screening is implemented in an increasing number of countries, usually in a two-step approach consisting in a noninvasive test followed by colonoscopy in case of a positive result. Prevalence of preclinical colorectal cancer strongly affects screening efficiency, but such data is scarce. Here, the authors provide detailed age- and sex-specific preclinical CRC prevalence estimates for various countries and geographical regions and show their implications on expected positive and negative predictive values of existing and potential noninvasive screening tests. Knowledge of these predictive values should enhance the empirical basis for decisions on CRC screening tests and target populations.

Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination
Julia M.L. Brotherton, Sepehr N. Tabrizi, Samuel Phillips, Jan Pyman, Alyssa M. Cornall, Neil Lambie, Lyndal Anderson, Margaret Cummings, Diane Payton, James P. Scully, Marsali Newman, Raghwa Sharma, Marlon Saville, and Suzanne M. Garland

Although Australia was the first country to implement a fully government-funded vaccination program against human papilloma virus (HPV), it remains unclear what carcinogenic HPV types are most frequent. Here the authors performed a country wide analysis of HPV genotypes in 847 cervical cancers using laser-capture microdissection. Compared to international studies, HPV16/18 was more (71.8%) and HPV31/33/45/52/58 less frequent (14.8%) with specifically less HPV58 detected, providing important information for the use of current or broader spectrum vaccine types.

Thyroid neoplasia risk is increased nearly 30 years after the Chernobyl accident
Mykola Tronko, Alina V. Brenner, Tetiana Bogdanova, Victor Shpak, Valery Ollynyk, Elizabeth K. Cahoon, Vladimir Drozdovitch, Mark P. Little, Valeriy Tereshchenko, Galyna Zamotayeva, Galyna Terekhova, Lyudmila Zurnadzhi, Maureen Hatch, and Kiyohiko Mabuchi

Of particular concern following the 1986 accident at the Chernobyl nuclear power plant are long-term health effects in children and adolescents from the most affected areas who received substantial radiation doses to the thyroid from intake of radioactive iodine (I-131)-contaminated milk. To evaluate risk of thyroid neoplasia nearly 30 years following the accident, the authors conducted a fifth cycle of thyroid screening of the Ukrainian-American cohort during 2012–2015. They found that the excess risk of malignant and benign thyroid neoplasia persists nearly three decades after exposure and underscores the importance of continued follow-up to characterize long-term pattern of I-131 risk.

Development of Kras mutant lung adenocarcinoma in mice with knockout of the airway lineage-specific gene Gprc5a
Junya Fujimoto, Sayuri Nunomura-Nakamura, Yihua Liu, Wenhua Lang, Tina McDowell, Yasminka Jakubek, Dalia Ezzeddine, Joshua Kapere Ochieng, Jason Petersen, Gareth Davies, Junya Fukuoka, Ignacio I. Wistuba, Erik Ehli, Jerry Fowler, Paul Scheet, and Humam Kadara

The development of Kras-mutant lung adenocarcinoma (LUAD), the most common molecular subtype of lung cancer, is poorly understood. Previous research, however, implicates Gprc5a, a retinoid-inducible G-protein coupled receptor, in the emergence of late-onset LUAD. Using in vivo carcinogenesis models and whole-exome sequencing, this study shows that Gprc5a−/− mice develop spontaneous LUADs with somatic driver Kras mutations. Gprc5a−/− mice exposed to the tobacco carcinogen NNK experienced accelerated development of LUADs harboring co-occurring mutations in additional drivers that potentially cooperate with Kras to facilitate LUAD pathogenesis. These additional drivers may be viable targets for early therapeutic intervention in Kras-mutant LUAD.
Tribbles 2 mediates cisplatin sensitivity and DNA damage response in epithelial ovarian cancer
Daniel Kritsch, Franziska Hoffmann, Daniel Steinbach, Lars Jansen, Stella Mary Photini,
Mieczyslaw Gajda, Alexander S. Mosig, Jürgen Sonnemann, Sven Peters, Margarita Melnikova,
Jürgen Thomale, Matthias Dürst, Ingo B. Runnebaum, and Norman Häfner

Many patients with epithelial ovarian cancer (EOC) experience remission following first-line chemotherapy, though the majority suffer relapse with chemoresistant tumors. Changes in DNA methylation patterns on genes dictating chemosensitivity are thought to influence this process. Here, Tribbles 2 (TRIB2), a pseudokinase of unknown function, was found to be hypermethylated and downregulated during cisplatin resistance development. In ovarian cancer cells, TRIB2-mediated sensitivity to cisplatin and other DNA-damaging agents via induction of G2/M cell cycle arrest and apoptosis. EOC Type II patients with low TRIB2-expressing tumors had reduced progression-free survival, suggesting that TRIB2 may be an important prognostic marker in EOC.

MicroRNA 375 regulates proliferation and migration of colon cancer cells by suppressing the CTGF-EGFR signaling pathway
Khondoker Jahengir Alam, Ji-Su Mo, Seol-Hee Han, Won-Cheol Park, Hun-Soo Kim, Ki-Jung Yun,
and Soo-Cheon Chae

In the search for a deeper understanding of molecular mechanisms underlying tumorigenesis in colorectal cancer (CRC), microRNAs have emerged as intriguing players. In particular, miR375, which is significantly downregulated in CRC, is of interest for its potential involvement in CRC suppression. This study suggests that connective tissue growth factor (CTGF), a signaling modulator activated in CRC tumorigenesis, is a direct target gene of miR375. In CRC cells, miR375 overexpression was found to downregulate EGFR signaling pathways via direct CTGF downregulation. Both in vitro and in vivo, miR375 overexpression regulated cell proliferation, angiogenesis, and cell death, functions relevant to tumor suppression.

TGF-β induced PAR-1 expression promotes tumor progression and osteoclast differentiation in giant cell tumor of bone
Ting Wang, Jian Jiao, Hao Zhang, Wang Zhou, Zhenxi Li, Shuai Han, Jing Wang, Xinghai Yang,
Quan Huang, Zhipeng Wu, Wangjun Yan, and Jianru Xiao

Protease activated receptor 1 (PAR-1) is overexpressed in several tumors and also plays a critical role in bone remodeling. Here the authors find PAR-1 overexpressed in giant cell tumor of bone and uncover a critical upstream role of TGF-β in PAR-1 overexpression. Inhibition of PAR-1 suppressed tumor growth, angiogenesis and osteoclastogenesis in giant cell tumor models both in vitro and in vivo, implicating PAR-1 causally in this generally benign condition that exhibits a high local recurrence rate.

Cyclin K dependent regulation of Aurora B affects apoptosis and proliferation by induction of mitotic catastrophe in prostate cancer
Sabrina Schecher, Britta Walter, Michael Falkenstein, Stephan Machner-Goeppinger,
Philipp Stenzel, Kristina Krümpelmann, Boris Hadaschik, Sven Perner, Glen Kristiansen,
Stefan Duensing, Wilfried Ruth, and Katrin E. Tagscherer

Cell cycle progression genes represent a promising source for biomarker discovery in prostate cancer, though little is known about their role in the disease. This study shows in prostate cancer cells that depletion of Cyclin K, a cell cycle regulator, is associated with apoptosis and inhibition of proliferation. The effects of Cyclin K downregulation were linked to Cyclin K dependent and Aurora B-mediated induction of mitotic catastrophe. In patients treated with adjuvant therapy, Cyclin K expression was associated with reduced biochemical recurrence-free survival. The results warrant further investigation of Cyclin K as predictive biomarker in prostate cancer.
1654  The clinical impact of tumour-infiltrating lymphocytes in colorectal cancer differs by anatomical subsite: A cohort study
Jonna Berntsson, Maria C Svensson, Karin Leandersson, Björn Nodin, Patrick Micke, Anna H Larsson, Jakob Eberhard, and Karin Jirström

In colorectal cancer, elevated levels of tumor-infiltrating lymphocytes in the tumor and its microenvironment are associated with improved survival. Whether this prognostic benefit differs according to tumor location, however, is unknown. Here, the prognostic impacts of CD3⁺, CD8⁺ and FoxP3⁺ tumor-infiltrating T cells were examined with respect to tumor location. The data link high CD8⁺ density with favorable prognosis for right-sided tumors, high FoxP3⁺ density to improved prognosis for rectal tumors and CD3⁺ density with improved prognosis for right colon and rectal tumors. Knowledge of variable immune system responses by tumor location could help inform the development of immune-modulating therapies.

1667  HPV circulating tumor DNA to monitor the efficacy of anti-PD-1 therapy in metastatic squamous cell carcinoma of the anal canal: A case report
Luc Cabel, François-Clément Bidard, Vincent Servois, Wulfran Cacheux, Pascale Mariani, Emanuela Romano, Mathieu Minsat, Ivan Bieche, Fereshteh Farkhondeh, Emmanuelle Jeannot, and Bruno Buecher

Immune checkpoint inhibitors emerged as a promising strategy against squamous cell carcinoma of the anal tract, a cancer associated with high-risk human papilloma virus (HPV) infection. However, the radiological evaluation of treatment success is often hampered by tumor pseudo-progression due to immune infiltration. Here the authors performed synchronous monitoring of blood HPV DNA levels during therapy using droplet-digital PCR, uncovering the potential of circulating viral DNA as a useful biomarker for treatment success in anal cancer.

1671  Therapeutic targeting of chemoresistant and recurrent glioblastoma stem cells with a proapoptotic variant of oncolytic herpes simplex virus
Nusrat Jahan, Jae M. Lee, Khalid Shah, and Hiroaki Wakimoto

Genetically modified oncolytic herpes simplex virus is one of the most extensively investigated oncolytic viruses and safe to administer to the brain. Here the authors used a modified form that expresses the proapoptotic factor TRAIL to test its efficacy in preclinical glioblastoma models resistant to chemotherapy. They demonstrate robust and selective induction of apoptosis-mediated death in tumor cells and a 40% cure rate in mice carrying chemotherapy-resistant intracerebral glioblastoma pointing to potential clinical applications in the future.

1682  DS-8201a, a new HER2-targeting antibody–drug conjugate incorporating a novel DNA topoisomerase I inhibitor, overcomes HER2-positive gastric cancer T-DM1 resistance
Naoki Takegawa, Yoshikane Nonagase, Kimio Yonesaka, Kazuko Sakai, Osamu Maenishi, Yusuke Ogihara, Takao Tamura, Kazuto Nishio, Kazuhiko Nakagawa, and Junji Tsurutani

In certain cancers, amplification and dysregulation of the human epidermal growth factor receptor HER2 is associated with more aggressive disease and worse prognosis, making it an appealing therapeutic target. Of special clinical interest in this regard is the antibody–drug conjugate (ADC) DS-8201a, which consists of an anti-HER2 antibody, a peptide linker, and an exatecan-derivative topoisomerase I inhibitor (Dxd). In the current preclinical study with gastric cancer cells, DS-8201a was found to overcome resistance to T-DM1, an established HER2-targeting ADC, by upregulating the ATP-binding cassette transporters ABCB2 and ABCG2. Moreover, the DS-8201a Dxd payload successfully inhibited the growth of T-DM1-resistant cells.
Connexin 43 upregulation by dioscin inhibits melanoma progression via suppressing malignancy and inducing M1 polarization

Yu Kou, Liyan Ji, Haojia Wang, Wensheng Wang, Hongming Zheng, Juan Zou, Linxin Liu, Xiaoxiao Qi, Zhongqiu Liu, Biaoyan Du, and Linlin Lu

New results reveal how an Chinese herbal medicine component acts against melanoma. Dioscin, a natural steroidal saponin, induces apoptosis in breast cancer as well as boosting production of pro-inflammatory cytokines. These authors investigated the chemical's effect on connexin 43, a tumor suppressing protein found in the microenvironment that is frequently silenced in metastatic melanoma. Dioscin remarkably enhanced the expression of connexin 43, as well as boosting its ability to reverse the metastatic transition. Treatment with dioscin also enhanced the immune response, spurring macrophages to attack the tumor cells.

Letter to the Editor

Early impact of the Japanese immunization program implemented before the HPV vaccination crisis

Koji Matsumoto, Nobuo Yaegashi, Takashi Iwata, Kasumi Yamamoto, Minou Nagashima, Toshiaki Saito, Kimio Ushijima, Fumiaki Takahashi, Kiichiro Noda, and Hiroyuki Yoshikawa

Questionable method for estimating the influence of mammography screening on breast cancer mortality in the Netherlands

Philippe Autier and Mathieu Boniol

Authors’ reply to: “Questionable method for estimating the influence of mammography screening on breast cancer mortality in the Netherlands”

V.D.V. Sankatsing, N.T. van Ravesteyn, E.A.M. Heijnsdijk, and H.J. de Koning

Retraction

Retraction

Cover Illustration: In this issue, the study by Fujimoto et al studied the role of G protein-coupled receptor class C group 5 member A (Gprc5a) loss in the mouse on the molecular pathology of lung malignancy. The same study also underscored previously uncharacterized expression patterns for Gprc5a in normal lung. Shown here is restricted and co-localized expression of Gprc5a with the alveolar type I (AT1) cell-specific marker podoplanin (Pdpn). These findings point to airway-lineage expression patterns for Gprc5a in the lung where the gene is specifically expressed in AT1 cells. See the related article by Fujimoto et al., pages 1589–1599.