

Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma

Sasha Bernatsky,¹ Héctor A Velásquez García,² John J Spinelli,² Patrick Gaffney,³ Karin E Smedby,⁴ Rosalind Ramsey-Goldman,⁵ Sophia S Wang,⁶ Hans-Olov Adami,^{7,8} Demetrius Albanes,⁹ Emanuele Angelucci,¹⁰ Stephen M Ansell,¹¹ Yan W Asmann,¹² Nikolaus Becker,¹³ Yolanda Benavente,¹⁴ Sonja I Berndt,⁹ Kimberly A Bertrand,¹⁵ Brenda M Birmann,¹⁶ Heiner Boeing,¹⁷ Paolo Boffetta,¹⁸ Paige M Bracci,¹⁹ Paul Brennan,²⁰ Angela R Brooks-Wilson,²¹ James R Cerhan,²² Stephen J Chanock,⁹ Jacqueline Clavel,²³ Lucia Conde,²⁴ Karen H Cotenbader,²⁵ David G Cox,²⁶ Wendy Cozen,²⁷ Simon Crouch,²⁸ Anneclaire J De Roos,²⁹ Silvia de Sanjose,^{14,30} Simonetta Di Lollo,³¹ W Ryan Diver,³² Ahmet Dogan,³³ Lenka Foretova,³⁴ Hervé Ghesquière,³⁵ Graham G Giles,^{36,37} Bengt Glimelius,³⁸ Thomas M Habermann,³⁹ Corinne Haioun,⁴⁰ Patricia Hartge,⁹ Henrik Hjalgrim,⁴¹ Theodore R Holford,⁴² Elizabeth A Holly,¹⁹ Rebecca D Jackson,⁴³ Rudolph Kaaks,¹³ Eleanor Kane,²⁸ Rachel S Kelly,¹⁶ Robert J Klein,⁴⁴ Peter Kraft,⁸ Anne Krickler,⁴⁵ Qing Lan,⁹ Charles Lawrence,⁴⁶ Mark Liebow,¹¹ Tracy Lightfoot,²⁸ Brian K Link,⁴⁷ Marc Maynadie,⁴⁸ James McKay,²⁰ Mads Melbye,⁴¹ Thierry J Molina,⁴⁹ Alain Monnereau,²³ Lindsay M Morton,⁹ Alexandra Nieters,⁵⁰ Kari E North,⁵¹ Anne J Novak,¹¹ Kenneth Offit,⁵² Mark P Purdue,⁵³ Marco Rais,⁵⁴ Jacques Riby,²⁴ Eve Roman,²⁸ Nathaniel Rothman,⁹ Gilles Salles,⁵⁵ Gianluca Severi,⁵⁶ Richard K Severson,⁵⁷ Christine F Skibola,²⁴ Susan L Slager,²² Alex Smith,²⁸ Martyn T Smith,⁵⁸ Melissa C Southey,⁵⁹ Anthony Staines,⁶⁰ Lauren R Teras,³² Carrie A Thompson,¹¹ Hervé Tilly,⁶¹ Lesley F Tinker,⁶² Anne Tjønneland,⁶³ Jenny Turner,⁶⁴ Claire M Vajdic,⁶⁵ Roel C H Vermeulen,⁶⁶ Joseph Vijai,⁵² Paolo Vineis,⁶⁷ Jarmo Virtamo,⁶⁸ Zhaoming Wang,⁶⁹ Stephanie Weinstein,⁹ Thomas E Witzig,¹¹ Andrew Zelenetz,⁵² Anne Zeleniuch-Jacquotte,⁷⁰ Yawei Zhang,⁷¹ Tongzhang Zheng,⁷² Mariagrazia Zucca,⁷³ Ann E Clarke⁷⁴

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For numbered affiliations see end of article.

Correspondence to

Dr Sasha Bernatsky;
Sasha.bernatsky@mcgill.ca

ABSTRACT

Objective: Determinants of the increased risk of diffuse large B-cell lymphoma (DLBCL) in SLE are unclear. Using data from a recent lymphoma genome-wide association study (GWAS), we assessed whether certain lupus-related single nucleotide polymorphisms (SNPs) were also associated with DLBCL.

Methods: GWAS data on European Caucasians from the International Lymphoma Epidemiology Consortium (InterLymph) provided a total of 3857 DLBCL cases and 7666 general-population controls. Data were pooled in a random-effects meta-analysis.

Results: Among the 28 SLE-related SNPs investigated, the two most convincingly associated with risk of DLBCL included the CD40 SLE risk allele rs4810485 on chromosome 20q13 (OR per risk allele=1.09, 95% CI 1.02 to 1.16, p=0.0134), and the HLA SLE risk allele rs1270942 on chromosome 6p21.33 (OR per risk allele=1.17, 95% CI 1.01 to 1.36, p=0.0362). Of additional possible interest were

rs2205960 and rs12537284. The rs2205960 SNP, related to a cytokine of the tumour necrosis factor superfamily TNFSF4, was associated with an OR per risk allele of 1.07, 95% CI 1.00 to 1.16, p=0.0549. The OR for the rs12537284 (chromosome 7q32, IRF5 gene) risk allele was 1.08, 95% CI 0.99 to 1.18, p=0.0765.

Conclusions: These data suggest several plausible genetic links between DLBCL and SLE.

Several recent studies have highlighted an increased risk of haematological malignancies, particularly non-Hodgkin's lymphoma (NHL), in patients with SLE.^{1 2} The determinants of the increased risk of NHL in SLE are unclear. The most common type of NHL in SLE (as in the general population) is the diffuse large B-cell lymphoma (DLBCL)

subtype. Using data from a recent NHL genome-wide association study (GWAS),³ our objective was to determine if certain SLE-related single nucleotide polymorphisms (SNPs) were also associated with the risk of DLBCL.

We focused on 28 SNPs independently associated with SLE in European Caucasians.⁴ All of these SNPs have been strongly associated with lupus risk, with a p value of 1×10^{-7} or stronger. Our hypothesis was that these SNPs would also be associated with DLBCL risk.

METHODS

GWAS data on European Caucasians from the International Lymphoma Epidemiology Consortium (InterLymph <http://www.epi.grants.cancer.gov/InterLymph>) studies and participating cohort studies were based on a total of 3857 DLBCL cases and 7666 controls. Each participating study's investigators obtained approval from human subjects review committees and informed consent from all participants. De-identified data were provided by the InterLymph Data Coordinating Center (Mayo Clinic, Rochester, Minnesota, USA).

For each SLE-related SNP, the ORs and 95% CIs were computed using a log-additive logistic regression model. Results from three previously conducted DLBCL GWAS studies were pooled in a random-effects meta-analysis. With 28 comparisons, an α of 0.05 would correspond to a Bonferroni-corrected p value of 0.0018.

RESULTS

Among the 28 SLE-related SNPs investigated (table 1), the two most convincingly associated with risk of DLBCL when correcting for multiple comparisons included the CD40 SLE risk allele rs4810485 on chromosome 20q13 (OR per risk allele=1.09, 95% CI 1.02 to 1.16, p=0.0134) and the HLA SLE risk allele rs1270942 on chromosome 6p21.33 (OR per risk allele 1.17, 95% CI 1.01 to 1.36, p=0.0362). Two other SNPs were of additional possible interest in DLBCL, with 95% CIs that just barely included the null value. The rs2205960 SNP, related to a cytokine of the tumour necrosis factor superfamily TNFSF4, was associated with an OR per risk allele of 1.07, 95% CI 1.00 to 1.16, p=0.0549. The OR for the SLE interferon regulatory factor (IRF5) risk allele

Table 1 SLE-related single nucleotide polymorphisms (SNPs) and ORs for diffuse large B-cell lymphoma (DLBCL) in European Caucasians in InterLymph data

Gene	Chromosome	SNP	Allele*		DLBCL OR	DLBCL 95% CI	p Value* DLBCL
			DLBCL SLE ref.				
<i>CD40</i>	20	rs4810485	T	T	C	1.088 (1.017 to 1.162)	0.013355
<i>HLA</i>	6	rs1270942	G	G	A	1.171 (1.010 to 1.357)	0.036172
<i>TNFSF4</i>	1	rs2205960	A	A	G	1.074 (0.998 to 1.156)	0.054899
<i>IRF5</i>	7	rs12537284	A	A	G	1.081 (0.992 to 1.179)	0.076450
<i>IL110</i>	1	rs3024505	A	A	G	1.102 (0.898 to 1.353)	0.352319
<i>BANK1</i>	4	rs10516487	A	A	G	1.035 (0.969 to 1.106)	0.303231
<i>Mir146a</i>	5	rs57095329	G	G	A	1.020 (0.756 to 1.377)	0.896089
<i>ITGAM</i>	16	rs9888739	T	T	C	1.008 (0.923 to 1.102)	0.851519
<i>IFIH1</i>	2	rs1990760	T	T	C	1.037 (0.978 to 1.101)	0.223359
<i>TNFAIP3</i>	6	rs7749323	A	A	G	1.053 (0.884 to 1.253)	0.564425
<i>NCF2</i>	1	rs17849502	T	G	G	1.050 (0.892 to 1.236)	0.554699
<i>STAT4</i>	2	rs7582694	G	C	C	1.110 (0.977 to 1.260)	0.108048
<i>PTPN22</i>	1	rs2476601	G	A	A	1.043 (0.937 to 1.161)	0.441704
<i>TYK2</i>	19	rs280519	G	A	A	1.016 (0.959 to 1.077)	0.582604
<i>PHRF1/IRF7/KIAA1542</i>	11	rs4963128	C	T	T	1.018 (0.956 to 1.085)	0.570646
<i>CD44</i>	11	rs507230	A	G	G	1.000 (0.941 to 1.062)	0.987988
<i>XKR6</i>	8	rs6985109	A	G	G	1.040 (0.981 to 1.103)	0.187826
<i>JAZF1</i>	7	rs849142	C	T	T	1.012 (0.903 to 1.134)	0.836267
<i>UBE2L3</i>	22	rs463426	C	G	T	1.060 (0.938 to 1.197)	0.349982
<i>BLK</i>	8	rs7812879	C	A	T	1.058 (0.956 to 1.172)	0.276113
<i>FCGR2A, FCGR3B</i>	1	rs1801274	G	T	A	1.023 (0.913 to 1.147)	0.693045
<i>IKZF1</i>	7	rs4917014	G	C	T	1.020 (0.916 to 1.138)	0.710394
<i>LYN</i>	8	rs7829816	G	C	A	1.031 (0.959 to 1.107)	0.411987
<i>TNIP1</i>	5	rs10036748	T	G	C	1.015 (0.950 to 1.085)	0.652213
<i>IRF8</i>	16	rs2280381	T	A	C	1.096 (0.933 to 1.287)	0.265341
<i>ATG5</i>	6	rs548234	T	G	C	1.033 (0.936 to 1.140)	0.518828
<i>PXK</i>	3	rs6445975	T	C	G	1.011 (0.945 to 1.083)	0.743076
<i>IL2/IL21</i>	4	rs907715	T	G	C	1.033 (0.967 to 1.104)	0.339144

*With 28 comparisons, an α of 0.05 would correspond to a Bonferroni-corrected p value of 0.0018.

rs12537284 (chromosome 7q32, gene) was 1.08, 95% CI 0.99 to 1.18, $p=0.0765$. A table presenting the study-specific contributions to the meta-analysis is provided in the online supplemental material.

DISCUSSION

Multiple studies have highlighted an increased risk of haematological malignancies, particularly NHL, in patients with SLE. To date, the reason for this excess risk has remained elusive. Recently, advances have been made in our understanding of lymphoma risk in other autoimmune rheumatic diseases, such as primary Sjögren's syndrome, where the majority of patients with mucosa-associated lymphoid tissue (MALT) lymphoma have either germline polymorphisms of TNFAIP3 related to the A20 protein important in nuclear factor κ B activation or somatic alterations of the gene within the lymphoma tissue.⁵ In their assessment of genetic risk overlap between rheumatoid arthritis (RA) and haematological cancers, Okada *et al*⁶ found that polymorphisms of TNFAIP3 were common to both RA and Hodgkin's lymphoma. Our analyses did not confirm a strong relationship with the lupus-related TNFAIP3 SNP rs7749323 specifically for DLBCL, but this may be a power issue, or may reflect the importance of different pathways for different haematological risk profiles across different autoimmune rheumatic diseases. Of note, our analyses were done in Caucasian populations; several non-Caucasian race/ethnic groups (eg, blacks, Asians) may have different genetic risk profiles and clinical presentations, thus future analyses could consider these populations as well. We have previously shown that the increased risk of lymphoma in SLE is similar across white, black and Asian patients.⁷ In addition, it may be that specific genetic risk factors for different clinical SLE manifestations may drive some of the risk of lymphoma, although we were unable to investigate that hypothesis here.

Existing data do suggest that some human leukocyte antigen (HLA) polymorphisms influence risk of DLBCL.⁸ In recent DLBCL GWAS analyses, HLA-B*08:01 reached genome-wide significance.⁴ In SLE, the strongest association in HLA is for the Class II allele DRB1*03:01. This allele is in strong linkage disequilibrium with HLA-B*08:01 in Caucasians so we are likely tagging the same HLA effect.⁹ CD40, a member of the tumour necrosis superfamily, plays a central role in regulating immune cells; CD40 is expressed on several B-cell neoplasms including DLBCL. Data have suggested a possible role for functional polymorphisms (specifically, C vs T, rs1883832) in the TNFRSF5 gene encoding CD40 in lymphomas originating within the germinal centre (both DLBCL and follicular).¹⁰ Tumour necrosis factor ligand superfamily involvement has been suggested in the pathology of malignant lymphomas.¹¹ Furthermore, in human NHL B-cell lines, IRF5 initiates a regulatory cascade by inducing the transcription factor activator protein 1 (AP-1) and cooperating with nuclear factor kappa B (NF- κ B), which appears

to represent a potentially important tumour promoting role of IRF5 in lymphoma.¹²

Not all of the excess risk of haematological malignancies in SLE is necessarily due to genetic factors; exposures within the environment may also be at play. However, in the InterLymph Subtypes pooling project, autoimmune diseases as a risk for lymphoma appeared to be independent of other potentially shared environmental risk factors (body mass index, sun, alcohol, occupation, etc).¹³ In the work of Ekström Smedby *et al*, SLE was associated with a 2.7-fold increase in risk of NHL risk overall; this was highest among patients with SLE of short duration (2–5 years), but a near twofold increase was also observed with more than 10 years of disease. Use of corticosteroid and immunosuppressive drugs categorically was not clearly linked to higher or lower risk, but analyses were not detailed.² Two very comprehensive case-control studies of SLE-related medications have suggested a link between cyclophosphamide (used intravenously in severe or resistant forms of SLE, especially nephritis) and haematological malignancies in general¹⁴ (and specifically, in lymphoma¹⁵). Fortunately, lymphoma after cyclophosphamide SLE treatment is a relatively uncommon outcome. Future studies of interactions between genetic factors and drug exposures may be warranted.

In conclusion, we studied a large GWAS datasets and found several plausible pathways linking DLBCL and SLE. Given that cyclophosphamide exposure in SLE is also associated with DLBCL risk, future studies might be able to explore whether these genetic risk factors may aid in risk stratification and decision-making when cyclophosphamide treatment is being considered for severe forms of SLE.

Author affiliations

¹Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, Canada

²BC Cancer Research Centre and School of Population and Public Health, University of British Columbia, Vancouver, Canada

³Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA

⁴Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, and Hematology Center, Karolinska University Hospital, Stockholm, Sweden

⁵Feinberg School of Medicine, Northwestern University, Chicago, USA

⁶Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, Duarte, USA

⁷Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

⁸Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA

⁹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA

¹⁰Hematology Unit, Ospedale Oncologico di Riferimento Regionale 'A. Businco', Cagliari, Italy

¹¹Department of Medicine, Mayo Clinic, Rochester, USA

¹²Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Jacksonville, USA

¹³Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

¹⁴Cancer Epidemiology Research Programme, Catalan Institute of Oncology-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

- ¹⁵Stone Epidemiology Center, Boston University, Boston, USA
- ¹⁶Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA
- ¹⁷Department of Epidemiology, German Institute for Human Nutrition, Potsdam, Germany
- ¹⁸The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA
- ¹⁹Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, USA
- ²⁰International Agency for Research on Cancer (IARC), Lyon, France
- ²¹Genome Sciences Centre, BC Cancer Agency, Vancouver, Canada
- ²²Department of Health Sciences Research, Mayo Clinic, Rochester, USA
- ²³Epidemiology of childhood and adolescent cancers Group, Inserm, Center of Research in Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris, France
- ²⁴Department of Epidemiology, School of Public Health and Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, USA
- ²⁵Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, USA
- ²⁶INSERM U1052, Cancer Research Center of Lyon, Centre Léon Bérard, Lyon, France
- ²⁷Department of Preventive Medicine, USC Keck School of Medicine, University of Southern California, Los Angeles, USA
- ²⁸Department of Health Sciences, University of York, York, UK
- ²⁹Department of Environmental and Occupational Health, Dornsife School of Public Health at Drexel University, Philadelphia, USA
- ³⁰CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
- ³¹Department of Surgery and Translational Medicine, Section of Anatomic Pathology, University of Florence, Florence, Italy
- ³²Epidemiology Research Program, American Cancer Society, Atlanta, USA
- ³³Departments of Laboratory Medicine and Pathology, Memorial Sloan Kettering Cancer Center, New York, USA
- ³⁴Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute and MF MU, Brno, Czech Republic
- ³⁵Department of Hematology, Centre Léon Bérard, Lyon, France
- ³⁶Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia
- ³⁷Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia
- ³⁸Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
- ³⁹Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, USA
- ⁴⁰Lymphoid Malignancies Unit, Henri Mondor Hospital and University Paris Est, Créteil, France
- ⁴¹Division of Health Surveillance and Research, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
- ⁴²Department of Biostatistics, Yale School of Public Health, New Haven, USA
- ⁴³Division of Endocrinology, Diabetes and Metabolism, The Ohio State University, Columbus, USA
- ⁴⁴Icahn Institute for Genomics and Multiscale Biology, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, USA
- ⁴⁵Sydney School of Public Health, The University of Sydney, Sydney, Australia
- ⁴⁶Westat Inc, Rockville, USA
- ⁴⁷Department of Internal Medicine, Carver College of Medicine, The University of Iowa, Iowa City, USA
- ⁴⁸Registre des Hémopathies Malignes de Côte d'Or, EA 4184, Univ. Bourgogne Franche-Comté and Dijon University Hospital, Dijon, France
- ⁴⁹Department of Pathology, AP-HP, Necker Enfants malades, Université Paris Descartes, Sorbonne Paris Cité, France
- ⁵⁰Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany
- ⁵¹Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, USA
- ⁵²Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA
- ⁵³Ontario Health Study, Toronto, Canada
- ⁵⁴Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Monserrato, Italy
- ⁵⁵Department of Hematology, Hospices Civils de Lyon, Pierre benite Cedex, France
- ⁵⁶Human Genetics Foundation, Turin, Italy
- ⁵⁷Department of Family Medicine and Public Health Sciences, Wayne State University, Detroit, USA
- ⁵⁸Division of Environmental Health Sciences, University of California Berkeley School of Public Health, Berkeley, USA
- ⁵⁹Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne, Melbourne, Australia
- ⁶⁰School of Nursing and Human Sciences, Dublin City University, Dublin, Ireland
- ⁶¹Centre Henri Becquerel, Université de Rouen, Rouen, France
- ⁶²Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA
- ⁶³Danish Cancer Society Research Center, Copenhagen, Denmark
- ⁶⁴Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia
- ⁶⁵Centre for Big Data Research in Health, University of New South Wales, Sydney, Australia
- ⁶⁶Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
- ⁶⁷MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK
- ⁶⁸Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland
- ⁶⁹Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
- ⁷⁰Department of Population Health, New York University School of Medicine, New York, USA
- ⁷¹Department of Environmental Health Sciences, Yale School of Public Health, New Haven, USA
- ⁷²Department of Epidemiology, Brown School of Public Health, Providence, USA
- ⁷³Department of Biomedical Science, University of Cagliari, Monserrato, Italy
- ⁷⁴Division of Rheumatology, University of Calgary, Calgary, Canada

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Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma

Sasha Bernatsky, Héctor A Velásquez García, John J Spinelli, Patrick Gaffney, Karin E Smedby, Rosalind Ramsey-Goldman, Sophia S Wang, Hans-Olov Adami, Demetrius Albanes, Emanuele Angelucci, Stephen M Ansell, Yan W Asmann, Nikolaus Becker, Yolanda Benavente, Sonja I Berndt, Kimberly A Bertrand, Brenda M Birmann, Heiner Boeing, Paolo Boffetta, Paige M Bracci, Paul Brennan, Angela R Brooks-Wilson, James R Cerhan, Stephen J Chanock, Jacqueline Clavel, Lucia Conde, Karen H Cotenbader, David G Cox, Wendy Cozen, Simon Crouch, Anneclaire J De Roos, Silvia de Sanjose, Simonetta Di Lollo, W Ryan Diver, Ahmet Dogan, Lenka Foretova, Hervé Ghesquières, Graham G Giles, Bengt Glimelius, Thomas M Habermann, Corinne Haioun, Patricia Hartge, Henrik Hjalgrim, Theodore R Holford, Elizabeth A Holly, Rebecca D Jackson, Rudolph Kaaks, Eleanor Kane, Rachel S Kelly, Robert J Klein, Peter Kraft, Anne Krickler, Qing Lan, Charles Lawrence, Mark Liebow, Tracy Lightfoot, Brian K Link, Marc Maynadie, James McKay, Mads Melbye, Thierry J Molina, Alain Monnereau, Lindsay M Morton, Alexandra Nieters, Kari E North, Anne J Novak, Kenneth Offit, Mark P Purdue, Marco Rais, Jacques Riby, Eve Roman, Nathaniel Rothman, Gilles Salles, Gianluca Severi, Richard K Severson, Christine F Skibola, Susan L Slager, Alex Smith, Martyn T Smith, Melissa C Southey, Anthony Staines, Lauren R Teras, Carrie A Thompson, Hervé Tilly, Lesley F Tinker, Anne Tjonneland, Jenny Turner, Claire M Vajdic, Roel C H Vermeulen, Joseph Vijai, Paolo Vineis, Jarmo Virtamo, Zhaoming Wang, Stephanie Weinstein, Thomas E Witzig, Andrew Zelenetz, Anne Zeleniuch-Jacquotte, Yawei Zhang, Tongzhang Zheng, Mariagrazia Zucca and Ann E Clarke

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