Male Factor Infertility and Health

Karen Baker, MD
Associate Professor
Duke University, Division of Urology
Fertility and...

- Cancer
- Heart disease
- Metabolic syndrome
- Diabetes
- Early death

- Goals:
  - Review literature linking MFI to poor health
  - Discuss possible mechanisms common to MFI and cancer
Cardiovascular risk

- 3.5 million AARP members surveyed 1995-1996
- 137,903 men met criteria
- 92% +paternity
  - mean age 62.7 yrs
  - 96.4% white
- Age adjusted cardiovascular mortality risk 2.7/1000 person-years
- Childless men 17%↑ cardiovascular mortality compared with men with + paternity

Eisenberg, Hum Repro 2011
Cardiovascular risk

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Eisenberg, Hum Repro 2011
Chronic disease

• Insurance claims 2001 - 2009
• 13,027 infertile men
  • Semen testing + MFI dx
• 23,860 fertile men
  • Semen testing  no MFI dx
• 79,099 vasectomy
  • Age
  • Smoking
  • Obesity

• Compared rates of common medical conditions
  • HTN, DM, peripheral vascular disease, cerebrovascular disease, ischemic heart disease, alcohol abuse, bipolar, etc.

Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data

Michael L. Eisenberg, M.D.,* Shufeng Li, M.S.,b Mark R. Cullen, M.D.,c and Laurence C. Baker, Ph.D.d
Chronic disease

• ↑ medical disease in MFI vs “semen testing” and vasectomies
  • DM HR 1.81 (95%CI 1.57-2.08)
  • Renal dz HR 1.6 (95%CI 1.14-2.24)
  • Peripheral vascular dz HR 1.52 (95% CI 1.12-2.07)
  • Ischemic heart dz HR 1.48 (95%CI 1.19-1.84)
Chronic disease

- 344 MFI university fertility center
  - “noninterracial couples”
- 293 consecutive age-matched fertile controls recruited from hospital
  - Age, BMI, education level, time to first conception, age at first conception
  - Charlson Comorbidity Index

Salonia, Eur Uro 2009
Chronic disease

- 344 MFI vs 293 controls
  - MFI
    - Longer to conceive
    - ↑ age at first conception
    - ↑ BMI
    - Lower educational status

<table>
<thead>
<tr>
<th></th>
<th>Infertile men</th>
<th>Fertile men</th>
<th>p* [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>344</td>
<td>293</td>
<td>-</td>
</tr>
<tr>
<td>Age at survey date, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.9 (6.4)</td>
<td>37.0 (5.2)</td>
<td>0.83 [t test]</td>
</tr>
<tr>
<td>Range</td>
<td>19–56</td>
<td>19–60</td>
<td>[−0.82–1.02]</td>
</tr>
<tr>
<td>Age at either first desired or actual conception of a pregnancy, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.9 (6.4)</td>
<td>31.3 (4.8)</td>
<td>0.0001 [t test]</td>
</tr>
<tr>
<td>Range</td>
<td>19–56</td>
<td>20–48</td>
<td>[5.08–6.99]</td>
</tr>
<tr>
<td>Period of time of either formal infertility or before conceiving a pregnancy, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.3 (7.5)</td>
<td>2.1 (3.3)</td>
<td>&lt;0.0001 [t test]</td>
</tr>
<tr>
<td>Range</td>
<td>13–89</td>
<td>0–12</td>
<td>[−20.13–18.27]</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>26.1 (4.0)</td>
<td>25.4 (3.0)</td>
<td>0.018 [t test]</td>
</tr>
<tr>
<td>Range</td>
<td>17.9–39.0</td>
<td>19.0–44.8</td>
<td>[0.12–1.22]</td>
</tr>
<tr>
<td>Educational status, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td>77 (22.4)</td>
<td>34 (11.6)</td>
<td>0.0005 [χ², 12.08]</td>
</tr>
<tr>
<td>HL</td>
<td>267 (77.6)</td>
<td>259 (88.4)</td>
<td>[5.07–16.53]</td>
</tr>
</tbody>
</table>

BMI = body mass index; LL = low level of education; HL = high level of education.
* p value according to χ² test or two-tailed student t test, as indicated.
Chronic disease

- 344 MFI vs 293 controls
  - MFI
    - 18.6% had comorbidity
    - vs 6.1% controls
Chronic disease

- 344 MFI vs 293 controls
  - MFI
    - 18.6% had comorbidity
      - vs 6.1% controls

### Chronic disease statistics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infertile</th>
<th>Fertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes - complication</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes + complication</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic Cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Chronic disease

• 183 MFI
  • Annual f/u for 10 years
  • Mean age 37
  • 24 men (14%) ↑ CCI >1 point
  • Cancer was the most common comorbidity
    • 11 solid organ, 1 lymphoma
      • Incidence of 6%
      • Age adjusted prevalence of cancer in Italian men 0.3%
MFI and cancer

- 20,433 men with semen analysis in UT 1996 – 2011
- 20,433 age matched controls
- Linked to population database and cancer registry
MFI and cancer

• 20,433 men with semen analysis in UT 1996 – 2011

• ↑testis CA
  • Oligospermia HR 11.9 (CI 4.9-28.8)
  • Normospermic HR 2.9 (CI 1.2-6.7)

Hanson Fertil Steril 2016
MFI and cancer

• 20,433 men with semen analysis in UT 1996 – 2011

• ↑ testis CA
  • Oligospermia HR 11.9 (CI 4.9-28.8)
  • Normospermic HR 2.9 (CI 1.2-6.7)

• Lowest quartile
  • Asthenospermia HR 4.1 (1.5-11.0)
  • Poor viability HR 6.6 (2.6-19.9)
  • Teratospermia HR 4.2 (1.4-12.5)
MFI and cancer

• 20,433 men with semen analysis in UT 1996 – 2011

• ↑testis CA
  • Oligospermia HR 11.9 (CI 4.9-28.8)
  • Normospermia HR 2.9 (CI 1.2-6.7)

• No association with azoospermia

• No association between prostate cancer and semen quality*
  • * mean age 32, mean follow up 7.3 yrs
MFI and cancer

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- ↑ testis CA
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Familial risks of MFI

Childhood Cancer Risk in the Siblings and Cousins of Men with Poor Semen Quality

Ross E. Anderson,* Heidi A. Hanson, William T. Lowrance, Jeffrey Redshaw, Siam Oottamasathien, Anthony Schaeffer, Erica Johnstone, Kenneth I. Aston, Douglas T. Carrell, Patrick Cartwright, Ken R. Smith and James M. Hotaling

- 10,511 men completed SA complete information on first degree relatives
- 10,511 fertile controls
  - 1:1 match age and birth year
  - ≥1 naturally conceived child
- Sibling and cousin data obtained through Utah Population database

Anderson, J Urol 2017
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- 10,511 fertile controls
  - 1:1 match age and birth year
  - >1 naturally conceived child
- Sibling and cousin data obtained through Utah Population database

**Subfertile men**
- Siblings: 32,141
- Cousins: 152,015

**Controls**
- Siblings: 31,740
- Cousins: 175,738
Familial risks of MFI

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• 10,511 subfertile men
• 10,511 fertile controls

• ↑ cancer siblings of oligospermia
  • HR 2.09 (CI 1.18-3.69)
• ↑ ALL siblings of oligospermia
  • HR 3.07 (CI 1.11-8.46)
• No association with
  • Other semen parameters
  • Brain cancer
  • Cousins

Table 3. Semen parameters and childhood cancer risk in siblings

<table>
<thead>
<tr>
<th>Model vs Fertile Controls</th>
<th>All Site</th>
<th>Acute Lymphoblastic Lymphoma</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azoospermia</td>
<td>1.37 (0.50–3.74)</td>
<td>1.66 (0.22–12.77)</td>
<td>1.84 (0.24–14.24)</td>
</tr>
<tr>
<td>Oligozoospermia</td>
<td>2.09 (1.18–3.69)</td>
<td>3.07 (1.11–8.46)</td>
<td>1.29 (0.29–5.83)</td>
</tr>
<tr>
<td>Normozoospermia</td>
<td>1.15 (0.78–1.68)</td>
<td>1.14 (0.51–2.53)</td>
<td>1.40 (0.62–3.16)</td>
</tr>
<tr>
<td>Hyperzoospermia</td>
<td>1.15 (0.74–1.78)</td>
<td>1.27 (0.52–3.10)</td>
<td>1.49 (0.59–3.78)</td>
</tr>
</tbody>
</table>

Anderson, J Urol 2017
Familial risks of MFI

- Men undergoing semen testing in UT 1996-2011
- “Fertile controls” Utah population database
  - Matched age + birth year
  - FDR (siblings)
  - SDR (aunts, uncles)
- Death certificate information
  - Death < age 20
Familial risks of MFI

• No association between poor semen quality and cancer mortality

• ↑ mortality from congenital malformations in siblings of men with MFI
  • Azoospermia HR 2.7 (CI 1.24 – 5.84)
  • Risk ↓ linearly as concentration ↑
    • ↑ age 1 – 5 years
    • ↑ female gender

Hanson, Hum Repro 2017
Semen parameters bellwether of male health

Temporal trends in sperm count: a systematic review and meta-regression analysis

Semen parameters bellwether of male health

Temporal trends in sperm count: a systematic review and meta-regression analysis


Levine, Hum Repro, 2017
Spermatogenesis

- Complex, multistep process
- DNA replication
- Meiosis
- DNA packaging
- Cellular reconfiguration
- Acquisition of motility

Spermatogenesis

• Complex, multistep process
  • DNA replication
  • Meiosis
  • DNA packaging
  • Cellular reconfiguration
  • Acquisition of motility

http://www.drgpbiology.com/spermatogenesis/
DNA repair the link?

• DNA repair is essential to somatic and genomic health
• Multiple mechanisms contribute to genomic fidelity
  • DNA polymerase proofreading
  • Mismatch repair (MMR)
  • Base excision repair (BER)
  • Nucleotide excision repair (NER)
  • Single strand break repair (SSBR)
  • Double strand break repair (DSBR)
Homologous recombination

• **Meiosis**
  • Genetic recombination
    • “crossing over”
  • Basis of genetic diversity

• **Somatic cells**
  • Double stranded DNA repair

• Errors in recombination activate checkpoint mechanisms
  • Meiotic arrest and cell death
DNA repair via NER

• Excision repair cross-complementing protein (ERCC1)
  • NER pathway
  • Homologous recombination
    • ERCC1-XPF complex removes single strand ends adjacent to regions of homology
    • Protect short telomeres

• Linked to multiple cancers
  • Colorectal, breast, gastric, gliomas, lung

• ↑expression → ↓response to cisplatin
DNA repair gene \textit{Ercc1} is essential for normal spermatogenesis and oogenesis and for functional integrity of germ cell DNA in the mouse

Kan-Tai Hsia\textsuperscript{1,*}, Michael R. Millar\textsuperscript{2}, Sasha King\textsuperscript{2}, Jim Selfridge\textsuperscript{1}, Nicola J. Redhead\textsuperscript{3}, David W. Melton\textsuperscript{3,*} and Philippa T. K. Saunders\textsuperscript{2}

- Strong ERCC1 expression in testis
DNA repair gene *Ercc1* is essential for normal spermatogenesis and oogenesis and for functional integrity of germ cell DNA in the mouse

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- Strong ERCC1 expression in testis
- Expression highest late pachytene to early spermatid
- ERCC1-/- mice had decreased testicular size
- Decrease seminiferous tubule size
- Decrease # germ cells
  - Areas of germ cell aplasia (SCO)
DNA repair gene *Ercc1* is essential for normal spermatogenesis and oogenesis and for functional integrity of germ cell DNA in the mouse.

- Strong ERCC1 expression in testis
- Expression highest late pachytene to early spermatid
- ERCC1-/- mice had decreased testicular size
- Decrease seminiferous tubule size
- Decrease # germ cells
- ↑ sperm DNA fragmentation

![DFI by ERCC1 genotype](image)
Mismatch repair (MMR)

• MMR proteins critical to DNA repair during replication
• Corrects errors of DNA polymerase that escape the 3’ → 5’ exonucleolytic proofreading activity
  • Recognize “daughter” strand
• MMR also critical to homologous recombination
Mismatch repair (MMR)

- Highly conserved
- “Mut” = inactivation causes hypermutable strains
- Heterodimers
  - MutS
    - MSH2 + MSH6
    - MSH2 + MSH3
  - MutL
    - MLH1 + PMS
    - MSH4 + MSH5
Mismatch repair (MMR)

- MMR is linked to Lynch syndrome
  - Germline mutation
  - ~4% colon cancer
    - MSH2 and MLH1 most common mutations

- Epigenetic silencing MLH1
  - ~10% colon cancer
Mismatch repair (MMR)

- ↓ germ cells
- + germ cell aplasia (SCO)

* Sertoli cell only

Paul 2007
Mismatch repair (MMR)

- ↓ germ cells
- + germ cell aplasia (SCO)
- ↓ seminiferous tubules

Mismatch repair (MMR)

- ↓ germ cells
- + germ cell aplasia (SCO)
- ↓ seminiferous tubules
- ERCC1-/-
  - ↑ apoptosis

Deletion of Genes Implicated in Protecting the Integrity of Male Germ Cells Has Differential Effects on the Incidence of DNA Breaks and Germ Cell Loss

Catriona Paul¹, Joanne E. Povey², Nicola J. Lawrence³, Jim Selfridge³, David W. Melton³, Philippa T. K. Saunders³

* p <0.05

Paul 2007
Mismatch repair (MMR)

• ↓ germ cells
• + germ cell aplasia (SCO)
• ↓ seminiferous tubules
• ERCC1-/-
  • ↑ apoptosis
  • ↓ epididymal sperm

Paul 2007 *** p <0.001
Mismatch repair (MMR)

- ↓ germ cells
- + germ cell aplasia (SCO)
- ↓ seminiferous tubules
- ERCC1-/-
  - ↑ apoptosis
  - ↓ epididymal sperm
  - ↑ sperm DFI
- ↔ MSH2 -/-

Deletion of Genes Implicated in Protecting the Integrity of Male Germ Cells Has Differential Effects on the Incidence of DNA Breaks and Germ Cell Loss

Paul 2007 ** p < 0.01
Changes in the Expression Profile of the Meiosis-Involved Mismatch Repair Genes in Impaired Human Spermatogenesis

ERNEST TERRIBAS,* § SANDRA BONACHE,* MARTA GARCÍA-ARÉVALO,* JOSVANY SÁNCHEZ,† ELADIO FRANCO,‡ LLUIS BASSAS,† AND SARA LARRIBA*
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• 13 severe MFI vs 5 GCT vs 10 controls
  • RT-PCR
    • MLH1, MLH3, PMS2, MSH4, MSH5

• ↓ expression MMR in severe MFI

![Graph showing expression ratio of MMR genes in MFI and fertile controls.]

* p<0.05
** p<0.01
*** p<0.001
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• 13 severe MFI vs 5 GCT vs 10 controls
  • RT-PCR
    • MLH1, MLH3, PMS2, MSH4, MSH5

• ↓ expression correlated with degree of spermatogenic dysfunction
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• 13 severe MFI vs 5 GCT vs 10 controls
  • RT-PCR
    • MLH1, MLH3, PMS2, MSH4, MSH5

• ↓ expression MMR in testis tumors

![Expression ratio chart]

<table>
<thead>
<tr>
<th>Gene</th>
<th>Expression Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>1.5</td>
</tr>
<tr>
<td>MLH3</td>
<td>2.0 **</td>
</tr>
<tr>
<td>PMS2</td>
<td>1.0 *</td>
</tr>
<tr>
<td>MSH4</td>
<td>2.5 **</td>
</tr>
<tr>
<td>MSH5</td>
<td>1.5 **</td>
</tr>
</tbody>
</table>

* p<0.05  
** p<0.01  
*** p<0.001
MMR

- 1,292 infertile males
  - 268 NOA
  - 256 oligospermia
  - 768 idopathic MFI
MMR

- 1,292 infertile males
- 480 controls
  - Semen parameters
  - Genotype MMR genes
    - MLH1, MLH3, PMS2, MSH4, MSH5
  - Sperm DNA fragmentation
  - Controlled for age, smoking, drinking
MMR

- 1,292 infertile males
- 480 controls
- Age NS
- Drinking NS
- ↑ % smokers in MFI
  - ↑ pack years

Common variants in mismatch repair genes associated with increased risk of sperm DNA damage and male infertility

Guixiang Ji1,2,3, Yan Long4, Yong Zhou5, Cong Huang1,2, Alhua Gu1,2* and Xinru Wang1,2*

Table 1 Distribution of selected characteristics between cases and fertile controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n = 480)</th>
<th>Case 1 (n = 524)</th>
<th>Case 2 (n = 768)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Age (mean ± SEM)</td>
<td>28.1 ± 0.16</td>
<td>28.3 ± 0.16</td>
<td>28.3 ± 0.14</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>278 (57.9)</td>
<td>238 (45.4)</td>
<td>363 (47.3)</td>
</tr>
<tr>
<td>Ever</td>
<td>202 (42.1)</td>
<td>246 (54.6)</td>
<td>405 (52.7)</td>
</tr>
<tr>
<td>Pack-years (mean ± SEM)</td>
<td>4.3 ± 0.21</td>
<td>5.2 ± 0.20</td>
<td>4.9 ± 0.14</td>
</tr>
<tr>
<td>Drinking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>425 (88.5)</td>
<td>447 (85.3)</td>
<td>667 (86.8)</td>
</tr>
<tr>
<td>Ever</td>
<td>55 (11.5)</td>
<td>77 (14.7)</td>
<td>101 (13.2)</td>
</tr>
<tr>
<td>Semen parameters (mean ± SEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration (× 10⁶/ml)</td>
<td>102.6 ± 3.07</td>
<td>5.12 ± 0.38</td>
<td>73.6 ± 2.12</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>65.3 ± 0.58</td>
<td>3.26 ± 0.27</td>
<td>37.9 ± 0.55</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>2.80 ± 0.07</td>
<td>2.37 ± 0.07</td>
<td>2.78 ± 0.05</td>
</tr>
<tr>
<td>Sperm DNA fragmentation (%)</td>
<td>n. d.</td>
<td>n. d.</td>
<td>19.3 ± 0.82</td>
</tr>
</tbody>
</table>

Case 1 = NOA + oligospermia
Case 2 = idiopathic MFI

Ji, BMC Medicine 2012
MMR

- 1,292 infertile males
- 480 controls
- MLH1, PMS2, MSH5
  - NOA and oligospermia
- PMS2
  - idiopathic MFI

Common variants in mismatch repair genes associated with increased risk of sperm DNA damage and male infertility

Guixiang Ji, Yan Long, Yong Zhou, Cong Huang, Alhua Gu, Xiru Wang

Table 3 Genotype frequencies of the four SNPs in MMR genes in patients and controls and their associations with male infertility risk

Case 1 = NOA + oligospermia
Case 2 = idiopathic MFI

Ji, BMC Medicine 2012
MMR

- 1,292 infertile males
- 480 controls

- MLH1, PMS2, MSH5
  - NOA and oligospermia
- PMS2
  - idiopathic MFI
- ↑ DFI
  - MLH1 and PMS2
But wait...what about chronic medical disease?

Nucleotide Excision DNA Repair Is Associated With Age-Related Vascular Dysfunction

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NER and vascular disease

- ERRC1 d/- vs WT mice
  - Truncated ERCC1 protein

- ↑ senescent vascular cells

- Accelerated ↓ vasodilator function
  - ↑ vascular stiffness
  - ↑ systolic pressure
  - ↑ pulse pressure
  - ↓ reactive hyperemia
Conclusion

• Poor semen parameters are bellwether of poor overall health

• DNA repair mechanisms are critical to genomic integrity
  • Meiosis period of vulnerability

• Defects in ERRC1 and various MMR proteins are associated with spermatogenic failure, cancer, and vascular disease

• Defects in DNA repair plausible link between MFI and significant medical comorbidities